

Case No. 2015-2021, -2022, -2023, -2024, -2025, -2026,
-2028, -2031, -2033, -2034, -2035, -2041, -2042, -2046,
-2047, -2049, -2059, -2060, 2016-1025, -1060, -1117, -1118

**UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT**

**ENDO PHARMACEUTICALS INC.,
GRUNENTHAL GMBH,**
Plaintiffs-Cross-Appellants,

v.

**TEVA PHARMACEUTICALS USA, INC., ACTAVIS
INC., ACTAVIS SOUTH ATLANTIC LLC,
WATSON PHARMACEUTICALS, INC., AMNEAL
PHARMACEUTICALS OF NEW YORK, LLC,
ROXANE LABORATORIES, INC., AMNEAL
PHARMACEUTICALS LLC, THORX
LABORATORIES, INC., BARR LABORATORIES,
INC., RANBAXY, INC., RANBAXY
PHARMACEUTICALS, INC., SUN
PHARMACEUTICAL INDUSTRIES, LTD.,
IMPAX LABORATORIES, INC.,**
Defendants-Appellants.

Appeals from the United States District Court for the Southern District of
New York in Nos. 1:12-cv-08060-TPG-GWG, 1:12-cv-08115-TPG-GWG,
1:12-cv-08317-TPG-GWG, 1:12-cv-08985-TPG-GWG, 1:13-cv-00435-TPG-
GWG, 1:13-cv-00436-TPG-GWG, 1:13-cv-03288-TPG, 1:13-cv-04343-TPG,
and 1:13-cv-08597-TPG, Senior Judge Thomas P. Griesa.

**APPELLANTS AMNEAL PHARMACEUTICALS OF NEW
YORK, LLC, AMNEAL PHARMACEUTICALS LLC,
IMPAX LABORATORIES, INC., THORX
LABORATORIES, INC., RANBAXY, INC., RANBAXY**

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Endo Pharmaceuticals Inc. et al. v. Teva Pharmaceuticals USA, Inc. et al.

Case No. 2015-2021 (lead consolidated)

CERTIFICATE OF INTEREST

Counsel for the Appellants Amneal Pharmaceuticals of New York, LLC and Amneal Pharmaceuticals LLC certifies the following:

1. Full name of Party Represented by me:

Amneal Pharmaceuticals of New York, LLC and Amneal Pharmaceuticals LLC

2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:

Amneal Pharmaceuticals of New York, LLC and Amneal Pharmaceuticals LLC

3. Parent corporations and publicly held companies that own 10% or more of stock in the party:

Amneal Pharmaceuticals LLC has one parent corporation, Amneal Pharmaceutical Holdings Company, LLC, and no publicly held company owns 10% (ten percent) or more of Amneal Pharmaceuticals LLC's stock. Amneal Pharmaceutical Holdings Company, LLC has one parent corporation, Amneal Holdings, LLC, and no publicly held company owns 10% (ten percent) or more of Amneal Pharmaceutical Holdings Company, LLC's stock. Amneal Holdings, LLC has no parent corporation, and no publicly held company owns 10% (ten percent) or more of Amneal Holdings, LLC's stock. Amneal Pharmaceuticals of New York, LLC is a wholly owned subsidiary of Amneal Pharmaceuticals LLC, and no publicly held company owns 10% (ten percent) or more of Amneal Pharmaceuticals of New York LLC's stock.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Endo Pharmaceuticals Inc. et al. v. Teva Pharmaceuticals USA, Inc. et al.

Case No. 2015-2021 (lead consolidated)

CERTIFICATE OF INTEREST

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1. Full name of Party Represented by me:

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2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:

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3. Parent corporations and publicly held companies that own 10% or more of stock in the party:

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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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Dated: October 3, 2016

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Endo Pharmaceuticals Inc. et al. v. Teva Pharmaceuticals USA, Inc. et al.

Case No. 2015-2021 (lead consolidated)

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Endo Pharmaceuticals Inc. et al. v. Teva Pharmaceuticals USA, Inc. et al.

Case No. 2015-2021 (lead consolidated)

CERTIFICATE OF INTEREST

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3. Parent corporations and publicly held companies that own 10% or more of stock in the party:

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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency

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/s/Carol Pitzel Cruz

Carol Pitzel Cruz

cc: Counsel of record

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Endo Pharmaceuticals Inc. et al. v. Teva Pharmaceuticals USA, Inc. et al.

Case No. 2015-2021 (lead consolidated)

CERTIFICATE OF INTEREST

Counsel for the Appellant Roxane Laboratories, Inc. certifies the following:

1. Full name of Party Represented by me:

Roxane Laboratories, Inc.

2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:

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3. Parent corporations and publicly held companies that own 10% or more of stock in the party:

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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

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Statement of Related Cases

Multiple appeals from related district court actions all involving Endo Pharmaceuticals Inc. (“Endo”), and sometimes also Grunenthal GMBH (“Grunenthal”), as plaintiffs, and various generic pharmaceutical companies as defendants, have been consolidated under the present lead appeal number. *See* caption. No appeal in or from any of the following cases was previously before this or any other appellate court:

Case No. 12-cv-8060 (S.D.N.Y.), *Endo and Grunenthal v. Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc.* (together “Teva”);

Case No. 12-cv-8115 (S.D.N.Y.), *Endo and Grunenthal v. Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York, LLC* (together “Amneal”);

Case No. 12-cv-8317 (S.D.N.Y.), *Endo and Grunenthal v. Impax Laboratories, Inc. and ThoRx Laboratories, Inc.* (together “Impax”);

Case No. 13-cv-435 (S.D.N.Y.), *Endo and Grunenthal v. Impax Laboratories, Inc.*;

Case No. 13-cv-436 (S.D.N.Y.), *Endo and Grunenthal v. Actavis Inc., Actavis South Atlantic LLC, and Watson Pharmaceuticals, Inc.* (collectively “Actavis”);

Case No. 13-cv-4343 (S.D.N.Y.) or No. 13-cv-8597 (S.D.N.Y.), *Endo v. Ranbaxy Inc., Ranbaxy Pharmaceuticals Inc. and Sun Pharmaceutical Industries, Ltd.* (collectively “Ranbaxy”).

Earlier appeals from Case No. 12-cv-8985 (S.D.N.Y.) and Case No. 13-cv-3288 (S.D.N.Y.) were previously before this Court in Appeal No. 2013-1658, *Endo v. Actavis, Inc. and Actavis South Atlantic, LLC*, and companion Appeal No. 2013-1662, *Endo v. Roxane Laboratories, Inc.* Those appeals were decided March 31, 2014, by Newman, Dyk, and Moore, Circuit Judges. The opinion is reported at *Endo Pharmaceuticals Inc. v. Actavis, Inc.*, 746 F.3d 1371 (Fed. Cir. 2014).

An appeal concerning the patent application that later issued as U.S. Patent No. 8,309,122 (“122 patent”), one of the patents at issue here, was previously before this Court in Appeal No. 2010-1307. That appeal was decided May 13, 2011, by Rader, Linn, and Moore, Circuit Judges. The opinion is reported at *In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011), which also decided related Appeal Nos. 2010-1308 and 2010-1309.

An appeal from an *inter partes* review (“IPR”) proceeding that involves U.S. Patent No. 8,329,216 (“216 patent”), the other patent at issue

here, is currently pending before this Court in Appeal No. 2016-1217,

Amneal v. Endo.

Introduction

This is a textbook case of obviousness. Oxymorphone has been a known and marketed drug for over a half a century. Although oxymorphone was marketed in immediate-release formulations, controlled-release formulations were disclosed in multiple prior art references and the delivery systems for such formulations were well known. All Endo did was to take a known compound (oxymorphone) and combine it with a known controlled-release delivery mechanism (the Penwest TIMERx system) to achieve the reasonably expected result. That effort is not “inventive”, nor can it support the validity of the ‘122 or ‘216 patent claims because “if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

The district court made several legal errors. First, the district court ignored this Court’s prior decision (in a case involving Endo with respect to the very application that matured into the ‘122 patent) holding that many of the core claim elements were disclosed in the prior art. The district

court ignored this Court's finding that the prior art Maloney reference, (Appx7591-7620), (1) "teaches a controlled release opioid formulation;" (2) discloses oxymorphone as "a preferred opioid compound"; (3) "would satisfy the claimed 12-hour effectiveness limitation"; and (4) "discloses a method of providing extended pain relief by the provision of a therapeutically effective amount of controlled release oxymorphone." *Kao*, 639 F.3d at 1071, 1072. Apparently convinced by Endo's irrelevant mantra at trial that Endo was the first company to physically manufacture and market its Opana® ER product (an extended release oxymorphone), the district court improperly ignored the explicit holdings of this Court and the ample disclosures in Maloney (and other prior art references presented at trial) to arrive at the contrary conclusion that there was no "motivation" to create a controlled-release oxymorphone formulation.

At trial there was no dispute that the delivery system used for Endo's alleged embodiment of the claimed controlled-release product pre-existed. In fact, Endo licensed that prior art controlled-release delivery system from Penwest. In an effort to make an obvious combination patentable, Endo baked into its claims ranges of dissolution rates (how much of the oxymorphone is released at different times when the formulation is put

into a liquid media and subjected to agitation) and inherent pharmacokinetic data (reflecting how oxymorphone is processed when put in the human body). But the dissolution limitations merely recite broad ranges of dissolution typical for a controlled-release product that numerous pieces of prior art teach a formulator would target – whether measuring dissolution with the USP Paddle or Basket method – to produce an oxymorphone formulation with 12-hour effect. Moreover, Endo never produced or tested formulations throughout the broad dissolution ranges claimed. To the extent the dissolution limitations are not simply obvious targets one of skill in the art would know to use to arrive at effective formulations through routine experimentation, then the claims are invalid for lack of written description because the inventors were not in possession of effective formulations throughout the full scope of dissolution parameters claimed.

The district court made errant and legally irrelevant findings regarding the pharmacokinetic data which Endo included in its claims – and once again ignored this Court in doing so. In *Kao*, certain “food effect” limitations present in the current patents were found to be “inherent” properties that add “nothing of patentable consequence.” 639 F.3d at 1070.

This Court went on to find that “Maloney’s express teachings render the claimed controlled release oxymorphone formulation [containing the food effect limitations] obvious.” *Id.* The district court also held that other measurements – which similarly reflect nothing more than inherent properties – could save the ‘122 and ‘216 patents from invalidity. They can’t. The law is clear that it “is not invention to perceive that the product which others had discovered had qualities they failed to detect.” *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (quoting *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945)).

Lastly, to the extent Endo disputes that the claimed food effect is inherent to the prior art, then the finding of infringement of the “food effect” claims cannot stand. Endo’s own expert testified that the accused products’ C_{\max} and AUC data could be “different” from the C_{\max} and AUC numbers for Endo’s product that he relied on to assume the accused products would infringe. Endo offered no actual evidence comparing the accused products to the asserted claims and did not meet its burden to prove infringement.

Jurisdictional Statement

The district court had jurisdiction over all the related actions under 28 U.S.C. § 1338(a). This Court has jurisdiction over all the consolidated appeals pursuant to 28 U.S.C. §§ 1292(a)(1), 1292(c), and 1295(a).

Statement of Issues

1. Whether the district court erred when it held that Defendants failed to show the asserted claims of U.S. Patent Nos. 8,309,122 and 8,329,216 are invalid as obvious under 35 U.S.C. § 103?
2. Whether the district court erred when it held that Defendants failed to show the asserted claims of U.S. Patent Nos. 8,309,122 and 8,329,216 are invalid for failing to meet the requirements of 35 U.S.C. § 112?
3. Whether the district court erred when it held that Endo met its burden to prove the asserted claims of U.S. Patent Nos. 8,309,122 and 8,329,216 containing “food effect” limitations, other than claims 40 and 42 of the ‘216 patent, infringed?

Statement of the Case and Facts

This appeal arises out of Endo's assertion of claims 2, 3, 19, and 20 of the '122 patent, and claims 1, 22, 40, 42, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 patent against the generic pharmaceutical defendants. *See* Appx18, Appx28, Appx62.¹ These formulation patents purportedly cover the formulation used in Endo's Opana® ER product, which is an extended release version of the opioid pain-reliever oxymorphone. *See* Appx6, Appx8202. The issues of infringement and invalidity relating to these patents were tried before Judge Thomas P. Griesa in the Southern District of New York. *See* Appx6. His rulings from that bench trial are the subjects of this appeal and Endo's cross-appeal.

A. This Court's *In re Kao* Decision

Long before the five-week trial conducted in the spring of 2015, this Court had made determinations about what certain prior art disclosed and the lack of contribution toward patentability of certain claim elements in Endo's patents. The '122 patent was issued from application 11/680,432

¹ Not all of the '216 patent claims were asserted against all of the Defendants. *See* Appx62 n.7, Appx73 n.10. For example, claims 57 and 79 were not asserted against Amneal. *Id.*; *see also* Appx8842 (table of claims asserted against each Defendant).

which, along with two other related applications, was the subject of *In re Kao*, 639 F.3d 1057 (Fed. Cir. 2011) (*reh'rg en banc denied*) (Appx6292-6309).

The '216 patent is a related application (a continuation of the parent application to the '122 patent). At issue in the *Kao* appeal was the patentability of certain claims then advanced by Endo. This Court examined the "Maloney" reference (WO 01/08661) which is also at issue in the present appeal.

The *Kao* appeal was brought to challenge the obviousness rejections that the U.S. Patent and Trademark Office and the Board of Patent Appeals and Interferences made with respect to the applications. All of the varied claims had been found obvious in view of "Maloney" in combination with another reference. *See Kao*, 639 F.3d at 1061-64. This Court affirmed all of the rejections in two applications, but remanded the application containing dissolution limitations for further proceedings. *Id.* at 1074. In doing so, this Court found that Maloney "discloses a method of providing extended pain relief by the provision of a therapeutically effective amount of controlled release oxymorphone" and "would satisfy the claimed 12-hour effectiveness limitation." *Id.* at 1071, 1072. This Court also agreed with the PTO that the inherent properties of controlled-release ("CR") oxymorphone

formulations taught by the prior art (including the “food effect”) could not add anything of “patentable consequence” to the claims. *Id.* at 1070; *see also id.* at 1072.

This Court recognized that Maloney discloses dissolution properties measured by the USP Basket Method, rather than the Paddle Method cited in the Endo patents. *See id.* at 1062, 1065-66; Appx7591-7620. This Court noted, however, that a finding of obviousness was not precluded simply because Endo’s claims recite a different dissolution measurement method than Maloney:

As an initial matter, it should be clear that it makes no difference, *a priori*, to the question of obviousness whether the hypothetical person of ordinary skill in the art would have understood the claimed dissolution profile in terms of a Paddle-Method or a Basket-Method test range, just as it would make no difference whether the hypothetical person of skill in the art preferred to think in English or Metric units. The claimed subject matter is not presumed to change as a function of how one elects to measure it.

Id. at 1066. The Court declined to hold that showing a correlation between the Paddle and Basket Methods would be necessary to establish obviousness, but rather left “for the Board to consider on remand” “the importance, *or lack thereof*, of the claimed range to the alleged non-obviousness of the invention.” *Id.* at 1067 (emphasis added).

Lastly, the Court indicated that Endo's secondary-considerations arguments could be rejected based on the lack of any nexus to the claimed invention and noted that Endo would have to prove a nexus between an aspect of its claims not inherent to CR oxymorphone formulations taught by the prior art to substantiate Endo's arguments. *Id.* at 1067-70. It further explained that "if the same behavior would be observed in any oxymorphone controlled release formulation, then there is no necessary nexus between the commercial success and the claimed formulation." *Id.* at 1069-70.

B. The '122 and '216 Patents

Despite this Court's finding in *Kao* that the core of the "invention" was known in the prior art and that pharmacokinetic data added "nothing of patentable consequence", 639 F.3d at 1070, the '122 and '216 patents ultimately issued. *See* Appx20073-20080, Appx9197-9205. Those patents generally relate to oral CR pharmaceutical formulations comprising oxymorphone (as well as methods of using the formulations), and the approved claims issued with various limitations reciting ranges of a dissolution profile and pharmacokinetic properties. Appx264-324.

Claim 19 of the '122 patent is exemplary of most asserted claims:

19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an *in vitro* dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

Appx291-292. All of the asserted claims contain limitations concerning the amount of drug released at certain time points in an *in vitro* dissolution test similar to those in claim 19 above, except for claim 1 of the '216 patent. *See* Appx291-292, Appx320-324. While claim 1 contains no “dissolution limitations,” it adds some inherent pharmacokinetic property limitations relating to blood plasma levels:

1. An oral controlled release oxymorphone formulation, comprising:
 - a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
 - b. a hydrophilic material,wherein upon oral administration of the formulation to a subject in need of an analgesic effect:

- (i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
- (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
- (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 \text{ to } \infty)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;
- (iv) the duration of the analgesic effect is through at least about 12 hours after administration; and
- (v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

Appx320. Some of the asserted claims also contain inherent pharmacokinetic limitations related to the “food effect” of oxymorphone. See Appx291-292, Appx320-324, *e.g.* at ‘216 patent claim 38 (“wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions”), claim 40 (“wherein the difference in the oxymorphone area under the curve $AUC_{(0 \text{ to } \infty)}$ between fed and fasted conditions is less than 20%”).

The other asserted claims all similarly contain only a few broad structural limitations (along with the dissolution and/or pharmacokinetic limitations discussed above). Appx291-292, at claims 2-3, 20 (and non-asserted independent claim 1) (tablet, comprising oxymorphone or salt thereof as sole active ingredient, controlled release delivery system with at

least one pharmaceutical excipient), claim 19 (tablet, comprising oxymorphone or salt thereof as sole active ingredient, controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid); Appx320-324 at claim 22 (and non-asserted independent claim 21) (tablet, oxymorphone or salt, one or more controlled release excipients), claims 40, 42 (and non-asserted independent claim 38) (solid oral dosage form, comprising about 5-80 mg oxymorphone or salt, controlled release delivery system), claims 50, 54 (and non-asserted independent claim 49) (pharmaceutical composition for oral delivery, controlled release delivery system, about 5-80 mg oxymorphone or salt), claims 57, 62, 64, 71 (and non-asserted independent claims 55, 66) (same plus tablet), claims 73, 74, 78, 79, 80, 82 (and non-asserted independent claims 72, 77) (“controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid”).

C. The Evidence at Trial

At trial, none of the fundamental disclosures were contested. It was admitted that oxymorphone was a long-known drug, that the controlled-release delivery system Endo used was a known prior art system, and that Endo merely combined the known drug with the known controlled-release delivery system in well-known ways. There was extensive testimony concerning the disclosures in Maloney and other prior art disclosing controlled-release systems.

1. Oxymorphone was a known opioid pain reliever

Oxymorphone is an opioid painkiller first approved for use in the U.S. in the late 1950s. Endo sold immediate-release (“IR”) versions of oxymorphone under the trade name “Numorphan.” Appx8, Appx90-91, Appx591-592, Appx660-661, Appx1880. In the 1970’s, sales of the tablet IR formulation ended for commercial reasons, but injectable and suppository IR oxymorphone formulations remained commercially available thereafter. Appx7-8, Appx91, Appx591-592, Appx660-661.

2. Penwest’s known controlled-release delivery system

It was uncontested that contract-developer Penwest had been marketing the controlled-release system utilized by Endo in its alleged

invention (called TIMERx) for many years before the '122 and '216 patent applications were filed. Appx1940-1942, Appx7447. That system was described in U.S. Patent No. 5,662,933 ("Baichwal") which teaches the specific CR hydrophilic matrix gelling agent delivery system used by Endo in its original commercial Opana® CR product.² Appx7535-7553. Penwest touted this delivery system as being suitable for a "broad range of orally administered drugs", including specifically oxymorphone. Appx7447 (Penwest prior art disclosing combining oxymorphone with known CR gelling agent matrix TIMERx to make CR oxymorphone formulation); *see also* Appx1896-1902, Appx1931, Appx1937-1945, Appx3162-3170, Appx7542 (prior art patent disclosing TIMERx CR systems suitable for use in conjunction with a wide variety of therapeutically active agents such as opioid analgesics), Appx8864-8865 (testimony from Penwest employee that TIMERx was designed and advertised to be a ready-to-use controlled-release system for use with a wide range of drugs).

The district court also heard evidence regarding the ease of using Penwest's "plug and play system":

² Endo sold its original formulation of Opana® ER between 2006-2012. In 2012 it launched a "crush-resistant" formula and discontinued selling the original formulation. *See* Appx12-13.

Basic processing steps are you take the drug, take the hydrophilic gel and just mix them, and then blend them or mix them, and then compress it into a tablet. That's how they are made, as simple as that.

Appx1902, Appx1941-1942.

Endo never contested that Penwest's prior art system disclosed all of the structural elements of the CR system claimed by Endo. The Court heard comparisons of the Baichwal patent's disclosure (for example claim 4 calling for a 1:1 ratio of xanthan gum to locust bean gum) to the disclosures in the '122 and '216 patents (table 1 of the '122 and '216 patents using the exact same gums in the exact same ratios). Appx1943-1944. The Baichwal patent also discloses that dissolution profiles within the ranges claimed by the '122 and '216 patents are typical for 12-hour products. For example, Table 12 reveals that examples 7 and 8 have dissolution ranges within the claim ranges of 15-50% after 1 hour (33.7% and 32.7%), 45-80% after 4 hours (63.9% and 60.3%) and at least 80% after 10 hours (85.6% and 82.3%).

Appx7547. Table 6 likewise teaches the same ranges for examples 3 and 4.

Appx7546, Appx1968-1969. Just as in the '122 and '216 patents, the Baichwal patent measured its dissolution ranges using the Paddle Method at 50 rpm. Appx1968, Appx7546. Indeed, the dissolution ranges in Endo's

claims merely encompass dissolution profiles typical for 12-hour controlled-release products. Appx1970; *see also* Appx1912-1913, Appx1959-1960, Appx1965-1972, Appx1975-1977, Appx2268-2274, Appx2291-2292, Appx7805-7807, Appx7812, Appx7981, A7983.

3. **Maloney**

Defendants presented multiple prior art references teaching CR oxymorphone formulations including the Maloney reference. Appx7591-7620. Consistent with the *Kao* opinion, the district court heard and saw that oxymorphone was identified and claimed as one of the “preferred” opioids to be used in the disclosed controlled-release formulations. Appx1931-1935, Appx7504, Appx7617 (claim 17), Appx7619 (claim 31). The court also heard that the dissolution profile disclosed in Table 8 for an oxycodone tablet fell within the ranges claimed in the Endo patents. Appx1959-1960, Appx7614. The measurements in Maloney were done using the Basket method at 100 rpm. Appx1964, Appx7603, Appx7605, Appx7612, Appx7614. Defendants also repeatedly brought the *Kao* decision concerning the Maloney disclosures to the attention of the district court. Appx514, Appx1932, Appx1995-1996, Appx2024, Appx2830-2831, Appx3421, Appx3433-3439, Appx8172-8173.

4. Oshlack

In addition to Maloney, the court was presented with U.S. Patent 5,958,452 (“Oshlack”), another prior art patent teaching (and in fact having issued claims to) CR oxymorphone formulations effective over at least 12 hours and reciting a target dissolution profile overlapping Endo’s claims. Appx1931, Appx1935-1937, Appx1958, Appx1965-1968, Appx2016, Appx2019, Appx7554-7590 (*see, e.g.*, 7:35-39 and claims 1, 10, 11, 23, 24, 25).

5. Other evidence

In addition to the disclosures mentioned above, the court also heard evidence regarding the structural similarity of oxymorphone to other opioids, including those previously used in controlled-release formulations with dissolution rates within the ranges in Endo’s claims. Appx1882-1885, Appx1898-1899, Appx1912-1913, Appx1959-1960, Appx1963-1972, Appx1975-1977, Appx2019, Appx2260-2274, Appx2291-2292, Appx7805-7806, Appx7812, Appx7981, A7983. There was also extensive testimony from a lifetime formulator regarding the development of the two USP-approved dissolution methods (the Paddle and Basket Methods) and the general understanding of one skilled in the art that, particularly in the context of CR formulations like at issue here, similar dissolution profiles

would be reported regardless of which method was used. Appx1904-1906, Appx1910-1911, Appx1972-1980, Appx2007-2008; *see also* Appx6429 (Madden prior art disclosing that hydrophilic matrix tablet CR formulations of highly soluble drugs (like the claimed CR oxymorphone formulations) produce “similar dissolution profile” regardless of whether dissolution is measured with USP apparatus I (basket) or II (paddle) and “irrespective of the degree of agitation”); Appx7494 (prior art Dissolution Handbook disclosing paddle and basket methods generally produce “roughly equivalent” dissolution).

D. The District Court’s Decision Regarding Validity of the Asserted ‘122 and ‘216 Patent Claims

After the bench trial, the district court held that all of the asserted claims of the ‘122 and ‘216 patents, except for claims 40 and 42 of the ‘216 patent, are infringed, Appx62-73,³ and that all the infringed claims are

³ The Defendants stipulated that most limitations of the asserted claims would be met by the accused pharmaceutical products described in Defendants’ ANDAs. The only disputed points as to infringement, relating to only some of the asserted claims, was whether Endo had met its burden to prove that the “food effect” limitations would be met by Defendants’ proposed ANDA products, and whether certain asserted method claims could be directly or indirectly infringed by Defendants. Appx8834-8849; *see also* Appx62-63. Because method claims 40 and 42 of the ‘216 patent require the separate steps of “providing a solid oral dosage form...” and

valid. Appx159. The district court rejected Defendants' obviousness, written description, and other defenses regarding the '122 and '216 patents. Appx89-129.⁴

The district court ruled that:

1) the prior art teaching of target dissolution rates for twelve-hour CR oxymorphone must be identical in method to support an obviousness finding, rather than simply teaching known dissolution rates for twelve-hour effect and giving a person of ordinary skill in the art ("POSA") a reasonable expectation of success.

2) even though the patentee tested only a narrow dissolution rate in the specification, its claims to much broader dissolution rates did not

"administering a single dose of the dosage form ...," the district court found there was not direct infringement by any single actor and that there was thus no indirect infringement by Defendants. Appx32-35, Appx60-62, Appx67-73.

⁴ Some Defendants' proposed crush-resistant CR oxymorphone ANDA products were also alleged to infringe another patent related to Opana® ER owned by Grunenthal, U.S. Patent No. 8,309,060. The district court held that the asserted claims of the '060 patent were infringed, but invalid. *See* Appx7, Appx73-85, Appx129-152. Plaintiffs originally asserted other patents, but only the '122, '216, and '060 were the subject of trial before the district court. *See* Appx14-15. Prior to trial, the district court ruled that U.S. Patent No. 8,114,383, another Grunenthal crush-resistance patent, was invalid based on collateral estoppel. *See id.* (citing Appx8500-8508).

violate the written description requirement.

3) the recitation of pharmacokinetic data (such as the blood levels or peaks) in the claims provides novelty, even if the claimed properties are simply the admitted inherent consequence of administering the drug and would also result from administering prior art drugs. *See generally id.*

Without even mentioning *Kao*, nor Maloney or Oshlack's explicit teachings that oxymorphone is one of a select few of preferred opioids for use in CR formulations, the district court concluded that using oxymorphone in a CR formulation was not obvious or taught by the prior art. Appx90-99; *cf.* Appx7591-7620, *e.g.* at p.13 (Appx7604) and claims 17, 31 (Maloney teaching oxymorphone as 1 of 13-14 preferred opioids for use in CR formulations); Appx7554-7590, *e.g.* at 7:35-39; claims 1, 10, 23, 24 (Oshlack teaching oxymorphone as 1 of 9 preferred opioids and claiming oxymorphone CR formulations effective over 12 hours).

The district court went on to conclude that even if a POSA were motivated to select oxymorphone for use in a CR formulation, the dissolution ranges recited in the '122 and 216 patents are not disclosed in the prior art. Appx99-106. In doing so, the district court again failed to acknowledge Oshlack's explicit claims to CR oxymorphone with

overlapping dissolution ranges. Appx99 (indicating Oshlack refers only to oxycodone); *cf.* Appx7587 claim 11 (and underlying claims 10, 7, 2, 1) (Oshlack claiming oxymorphone CR formulations within recited dissolution ranges). The district court also discounted the prior art's teaching of target dissolution ranges for effective CR opioid formulations simply because some of those references disclosed testing dissolution with the basket method at 100 rpm (or paddle method at 100 rpm) instead of the claimed paddle method at 50 rpm. Appx99-100, Appx103.

The district court held Defendants had not met their burden to prove the obviousness of the claims because:

it was incumbent on defendants to show two things at trial: (1) that a person of ordinary skill, upon reading the prior art, would understand oxymorphone to be interchangeable with other active ingredients in a controlled release delivery system; and (2) that the results of the dissolution testing methods used in the prior art could be read to indicate the results of the dissolution testing methods used in the Endo patents.

Appx100; *see also generally* Appx100-107. Thus, contrary to this Court's guidance, the district court required that Defendants must have shown "interchangeability" or a specific numerical "correlation" "equat[ing] the results" of dissolution results measured with the USP paddle and basket dissolution test methods at different speeds. Appx106-107.

Even though the district court indicated that claimed pharmacokinetic effects occur naturally as “the result of the body’s natural processes” following administration of a CR oxymorphone formulation, (Appx111), it still gave patentable weight to those pharmacokinetic limitations. Appx107-119. Because the district court thought the very idea of CR oxymorphone was not obvious and not taught by the prior art, it appeared to find the pharmacokinetic limitations significant as well. *See Appx107-119, e.g. at Appx111* (“These pharmacokinetic effects *are only possible* because the dosage form, the invention itself, slows the release of oxymorphone ...”).

The district court also held that secondary considerations supported its finding of non-obviousness. Appx119-122. It held that Endo demonstrated “a clear nexus between the asserted claims of the ‘122 and ‘216 patents and the market success of the branded products” because “key features of the invention include its twelve-hour dosing interval and analgesic effectiveness over the same period.” Appx119-120. But those are features of *any* 12-hour CR opioid analgesic product, not an inventive aspect of the asserted claims.

To support its rejection of Defendants' on-sale bar defense not at issue in this appeal, the district court adopted Endo's argument that it was not in possession of an invention "ready for patenting" until a full FDA clinical human subject study was conducted. Specifically, although evidence was presented that Endo had developed a formulation it called suitable for a 12-hour product with a dissolution profile falling within the claimed dissolution range limitations within only a few months of first exploring the idea of making a CR oxymorphone product, Appx663-681, the district court concluded Endo's claims were not ready for patenting until Endo years later completed an FDA-approved clinical study and finalized the final study report that indicated the single commercial Opana® ER formulation was "an effective analgesic." Appx122-125. Nevertheless, the district court summarily rejected Defendants' indefiniteness, non-enablement and written description defenses even though the specification does not describe formulations that fall anywhere close to the ends of the broadly claimed dissolution ranges, nor ever reference any supporting clinical data for any range outside of the narrow ranges listed in the specification. Appx125-128. For example, despite claiming a dissolution range of between 45 and 80% at 4 hours (a broad 35

percentage point range), Endo only presented data falling between the much narrower 8.8 percentage point range from 58.1 and 66.9%. Appx283 (Table 4). In addressing Defendants' written description argument, the court wrote:

A [POSA], upon reading the dissolution ranges, would understand that the inventors had chosen ranges encompassing the invention, and also allowing for variations. Indeed, had the claims been more restrictively drawn they would have invited infringement. ... [A POSA], upon reading [the broad dissolution ranges as claimed by Endo] would understand them to encompass the invention ... possessed by the inventor.

Appx128 (emphasis added).

Summary of Argument

The district court failed to cite, let alone acknowledge, the highly relevant precedent of this Court in *Kao*. In doing so, the district court (i) applied an incorrect legal standard for obviousness, and (ii) misapplied the teachings of relevant prior art, including failing to even acknowledge explicit content of prior art which disclosed the exact same subject matter that Endo now claims in the patents-in-suit. Instead, the district court was misled by Endo's red-herring arguments about low bioavailability of oxymorphone that this Court already recognized would not deter a POSA.

The Defendants proved by clear and convincing evidence that the asserted claims of the '122 and '216 patents would have been obvious. A POSA would have had the motivation and knowledge to formulate an effective CR oxymorphone composition as claimed by Endo. Indeed, the prior art Oshlack patent disclosed and claimed the same subject matter. A POSA following the prior art teachings of Oshlack, Maloney, or Baichwal and Penwest, and armed with standard knowledge of CR opioid analgesics, would have had a reasonable expectation of success in making the claimed subject matter.

The fact the prior art disclosures are “on paper” and do not necessarily evidence someone else physically making the CR oxymorphone formulations taught is of no legal import. The relevant legal standard is a reasonable likelihood of success. The district court failed to apply this standard, and instead was misled by Endo’s arguments to demand evidence of direct numerical correlation between USP paddle and basket dissolution testing results or interchangeability of oxymorphone into a different known drug formulation: neither of which is legally required.

Endo’s arguments, as adopted by the district court, also belie fundamental problems and an inconsistency exposing the invalidity of the asserted patent claims. Endo argued that the reduction to practice of its invention was the manufacturing of Opana® ER and subjecting that drug to clinical trials. In response to Defendants’ on-sale bar defense, Endo argued that its invention was not ready for patenting until *after* a clinical trial showed Endo’s commercial formulation produced effective analgesia for 12 hours. If that were the case, that Endo had its “invention” only after a clinical trial was run and its one commercial formulation exhibited 12-hour efficacy, then a POSA would not have understood that the inventors were in possession of the full scope of their patent claims.

The '122 and '216 patents explicitly claim functional limitations — *e.g.*, recitations of inherent pharmacokinetic properties of efficacy and dissolution properties within which *thousands* of formulations could fall — and little recitation of structure. If the prior art's teaching of how to make CR oxymorphone formulations effective for at least 12 hours does not render the purported inventions of the patents-in-suit obvious, then Endo's clinical testing of merely *one* formulation does not provide written description support of the full scope of its claims. If the art is so unpredictable that an "effective" formulation cannot be reasonably predicted without clinical efficacy test data, then Endo's testing of merely one formulation — and lack of disclosure of industry-standard efficacy-type testing — does not show possession of the entire genus of formulations functionally claimed. Endo's own lead inventor testified they had no idea if formulations with dissolution parameters at the low-end or high-end of its broad claimed dissolution ranges would be effective or not. Endo is not legally entitled to claims covering what its inventors conceded was not in their possession.

Argument

I. The District Court Erred In Its Obviousness Analysis.

Obviousness is a question of law based on underlying factual determinations, including the scope and content of the prior art, differences between prior art and the claims at issue, and the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). These factual determinations made at a bench trial are reviewed for clear error, while a district court's ultimate conclusion of obviousness is a question of law reviewed *de novo*. *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 858 (Fed. Cir. 2015).

A claim is obvious when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art” *Graham*, 383 U.S. at 13. “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416.

The district court erred in holding that Defendants failed to prove the asserted claims of the '122 and '216 patents are invalid.⁵ The district court erred by failing to apply the correct legal standard, ignoring this Court's directly relevant precedent in *Kao*, and disregarding explicit disclosures of the prior art. Applying the correct standard and crediting the unambiguous

⁵ Amneal, like other Defendants, contends the asserted claims are obvious. Endo filed a motion to strike Amneal's obviousness defense, asserting IPR2014-00360 estopped Amneal pursuant to 35 U.S.C. § 315(e)(2) at least as to the subset of asserted '216 patent claims at issue in this litigation that were also addressed in the PTAB's final decision. The district court denied that motion as moot. *See* Appx37085, Appx163, Appx8515. That motion was correctly denied. As the PTO and this Court have previously recognized, IPRs like IPR2014-00360 are "limited" proceedings that review only incomplete and arbitrarily-chosen evidence of obviousness, and thus estoppel under § 315 cannot be applied to preclude judicial review of grounds or evidence of obviousness going beyond the limited evidence reviewed in an IPR. *See HP Inc. v. MPHJ Tech. Invs., LLC*, 817 F.3d 1339, 1347-48 (Fed. Cir. 2016); *Shaw Indus. Group v. Automated Creel Sys.*, 817 F.3d 1293, 1300 (Fed. Cir. 2016); *see also Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016). The evidence presented before the district court went beyond the scope of evidence to which the PTAB arbitrarily limited its review. *See* pending Fed. Cir. Appeal No. 2016-1217. Thus, § 315 estoppel cannot apply here, even as to the claims that were the subject of the IPR. Moreover, Amneal's co-appellants are not estopped under § 315, so if the asserted claims here are found to be invalid based on the other Defendants' defenses, Amneal "may reap the benefit of the invalidity decision under principles of collateral estoppel." *Mendenhall v. Barber-Greene Co.*, 26 F.3d 1573, 1577 (Fed. Cir. 1994); *see also ePlus, Inc. v. Lawson Software, Inc.*, 789 F.3d 1349, 1355-56 (Fed. Cir. 2015) ("upholding injunctions [barring infringement of patents] would be 'anomalous in the extreme in connection with patents this court has just held invalid'" (quoting *Mendenhall*, 26 F.3d at 1578)).

disclosures (some of which were already explicitly recognized by this Court), there can be no doubt that the asserted '122 and '216 patent claims are obvious. Nor can the purported secondary considerations – which were never linked to any aspect of the claims not within the prior art despite this Court's directive in *Kao* – salvage the patents from invalidity.

A. The district court failed to acknowledge that explicit disclosures in the prior art, including disclosures this Court previously recognized, teach the use of oxymorphone in a controlled-release formulation.

The district court did not believe that there was a “motivation” to make a controlled-release formulation with oxymorphone. Appx98-99. Beyond the mere existence of a “motivation,” the district court was presented with prior art that unambiguously actually disclosed – and claimed – controlled-release oxymorphone formulations.

First, Maloney provided for “an improved solid, oral dosage formulation for the *in vivo* sustained release of opioid compounds, and salts thereof, and in particular for the sustained-release of opioid analgesics.” Appx7597. It made clear that “[p]referred opioid compounds useful in the present invention” include “oxymorphone.” Appx7604. In multiple claims of her patent, Maloney claimed dosage forms using

oxymorphone. *See* Appx7617 at claim 17, Appx7619 at claim 31. This Court previously recognized those very disclosures and found that Maloney “discloses a method of providing extended pain relief by the provision of a therapeutically effective amount of controlled release oxymorphone” and contains disclosures that “would satisfy the claimed 12-hour effectiveness limitation.” *Kao*, 639 F.3d at 1071, 1072. The district court’s failure to credit the Maloney reference or to even acknowledge (much less credit) this Court’s decision was clear error.

If Maloney was not enough, Oshlack claims the very same subject matter as the patents-in-suit: therapeutically or analgesically-effective CR oxymorphone formulations effective over at least 12 hours. Claim 10 specifically claims a sustained release pharmaceutical formulation” where the “therapeutically active agent” is “oxymorphone.” Appx7587 (*see also* underlying claims 7, 2 and 1). Claim 11, like most of the ‘122 and ‘216 patent claims at issue, further recites dissolution ranges for the claimed formulation where oxymorphone is effective for at least 12 hours. *Id.* Even Endo’s own expert, Dr. Fassihi, acknowledged on cross-examination at trial that prior art literature disclosed using oxymorphone in controlled-release formulations. Appx1174-1176.

Given the disclosures of Maloney and Oshlack specifically disclosing and claiming prior art formulations of controlled-release oxymorphone, there was no need to seek evidence of a “motivation” to create such a formulation. And if motivation was a requirement, Maloney and Oshlack unambiguously supplied one. Even without Maloney and Oshlack, there were explicit and public suggestions to make a controlled-release oxymorphone product. Penwest, a contract-developer who owned the TIMERx controlled-release delivery system, claimed that its system was “applicable to a broad range of orally administered drugs” and specifically discussed in public prior art efforts towards an “oral controlled release version of the narcotic analgesic oxymorphone.” Appx7447. Endo did not create a new and unique delivery system to carry oxymorphone. To the contrary, it merely went out and licensed an off-the-shelf delivery system to “invent” Opana® ER and break into the already growing CR opioid market with the opioid it was already selling in IR forms. Appx644-651, Appx658, Appx660-661, Appx1918-1923.

And even if there wasn't Maloney, Oshlack, and Penwest's own public promotion of its delivery system, there was nothing inventive in 2001 about making CR oxymorphone. At the time of the alleged invention:

(i) opioids, including oxymorphone, were well-known analgesic agents, and (ii) the benefits of, and motivation to make, CR formulations for opioid pain relievers, including oxymorphone, were well-known. Appx279 at 1:20-65, Appx1878-1882, Appx1887-1888, Appx1894-1896, Appx1957, Appx2137-2141, Appx2251-2252. In fact, multiple CR opioids were already on the market by 2001, such as MS Contin and Kadian (CR morphine), and OxyContin (CR oxycodone). Appx653, Appx2252, Appx2364, Appx6277-6280, Appx6419-6423, Appx7426-7429, Appx7435-7441, Appx7963. Thus, market pressure encouraged Endo to convert the long-known opioid oxymorphone into a CR form. “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.” *KSR*, 550 U.S. at 421.

Endo’s argument that the low bioavailability of oxymorphone would dissuade a POSA from making CR oxymorphone cannot erase the explicit disclosures discussed above, *see* Appx91-95, and is a red herring contradicted by those clear disclosures. For example, while Oshlack recognizes that bioavailability is a consideration when making CR compositions, Oshlack nonetheless claims oxymorphone as one of only

nine preferred opioids for its CR formulations. *See* Appx7587, *e.g.* at claim 10. Likewise, Maloney claimed oxymorphone as one of thirteen opioids preferred for use in its CR formulations. *See* Appx7617-7619 at claims 17, 31. This Court previously recognized that including opioids like oxymorphone in such short lists for claimed CR opioid formulations shows that a POSA would be motivated to select such a drug for use in a CR formulation. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 981-82 (Fed. Cir. 2010) (POSA “would have been motivated to make the claimed tramadol formulation in light of Oshlack’s listing of tramadol” as “Oshlack makes that very selection” in naming its short-list of preferred opioid drugs). The prior art – particularly Oshlack, Maloney and Penwest – amply illustrates that a POSA would have been motivated to make CR oxymorphone despite oxymorphone’s low bioavailability.

Moreover, this Court already considered and rejected the same “low bioavailability” argument that Endo continues to make. *Kao* held that Maloney “expressly teaches using oxymorphone in the disclosed formulations” and therefore shows that a POSA had a “reasonable expectation” of success in formulating effective (12-hour) CR oxymorphone regardless of oxymorphone’s low bioavailability. 639 F.3d at 1070-71. The

trial testimony explained why these low bioavailability “concerns,” *id.*, would not deter a POSA from making controlled-release oxymorphone: both parties’ technical experts testified that a POSA could simply raise the dosage amount of the opioid – exactly as Endo did – to address any low-bioavailability issue. Appx1882, Appx1947-1957, Appx3201-3204, Appx3215-3216. Even Endo’s inventor acknowledged that he was confident even before starting work that a CR oxymorphone could be made. Appx8907-8908.

Lastly, and despite Endo’s counsel’s repeated assertions and promises to the court that no CR formulation with as low a bioavailability as oxymorphone had ever been made before Endo’s alleged invention, Endo’s expert was forced to concede that oxybutynin had lower bioavailability than oxymorphone and was contained in a prior art (and FDA-approved) CR product. Appx3207-3210.⁶ The district court’s attempt to discount this evidence, which annihilates Endo’s cornerstone argument at trial, (Appx94-95), is contrary to the law. Even if CR formulations comprising active pharmaceutical ingredients having low bioavailability

⁶ Endo was undoubtedly aware of oxybutynin despite its counsel’s repeated arguments, as it was used by Endo as a surrogate drug in developing its CR formulation. Appx3207, Appx8905-8906.

were rare,⁷ that does not detract from the fact that such formulations were made and would have motivated a POSA to develop a similar formulation for oxymorphone in view of the relevant prior art. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (reasonable expectation of success established by single prior art reference suggesting likelihood of success of claimed formulation, despite plaintiff's evidence of general unpredictability of drug formulation and specific challenges); *see also Kao*, 639 F.3d at 1070-71.

B. Endo's recitation of broad dissolution ranges measured by specific technique in asserted claims does not change the obviousness of the claimed formulations.

The district court spent a great deal of time analyzing whether there were specific disclosures in the prior art of the specific dissolution protocols recited in asserted claims (USP Paddle at 50 rpm) and whether there was a specific numerical "correlation" between dissolution results measured with alternate measurement methods. It was, however, asking the wrong questions and looking for the wrong data. The district court failed to apply the correct standard for obviousness, acknowledge legally

⁷ However, the trial record included evidence of not just one, but several, "low" bioavailability CR drugs. Appx1954-1956, Appx7787-7788.

presumed-enabled prior art claiming the same subject matter, and credit evidence presented regarding the general relationship of the alternate dissolution protocols.

1. The district court failed to apply the appropriate analysis.

The district court committed further legal error when it placed the burden on Defendants to prove “interchangeability” or a specific numerical “correlation” “equat[ing] the results” of dissolution results measured using the USP paddle dissolution testing method, on the one hand, and USP basket dissolution testing method, on the other hand. Appx100-107. That is not the law.

The claimed dissolution limitations are merely functional (not structural) limitations which define the claimed tablets or formulations not by what they are, but by what they do, *i.e.*, dissolve at a rate somewhere within the broad claimed ranges. Here, the prior art disclosure of the structural elements of the claimed formulation created a *prima facie* case of obviousness. “[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness....” *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir.

1990) (*en banc*); see also *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (same); *In re Gleave*, 560 F.3d 1331, 1338 (Fed. Cir. 2009) (claims describing even unobvious properties of previously known compositions not patentable where the compositions were described in prior art).

The few structural limitations of the asserted claims are very broad and generic elements such as “tablet”, “about 5-80 mg oxymorphone or salt,” a “controlled release delivery system” with “one or more controlled release excipients,” or a “controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent” SOC, *supra* pp. 15-16. Endo did not challenge the teachings in the prior art of any of these elements, nor could it. These structural elements are the most basic ingredients in almost any prior-art CR opioid formulation (or with respect to the claimed amounts of oxymorphone merely what a POSA based on well-known conversion references would know were amounts of oxymorphone equivalent to amounts of other effective CR opioids). Appx1885-1886 (testimony regarding oxymorphone amounts); Appx1894-1902, Appx1944-1945, Appx1958, Appx1960-1961, Appx1963 (testimony regarding multiple broad structural limitations);

Appx1980-1985 (testimony regarding matrix with claimed percentages of gelling agent); Appx2024-2028 (testimony regarding oxymorphone amounts); Appx3216-3218; Appx7535-7553, *e.g.* at 6:37-44, 7:32-43 (prior art disclosing CR gelling matrix system with 10 – 75% gelling agent appropriate for use with numerous drugs such as opioids); Appx7554-7620 (additional prior art disclosing basic structures claimed by Endo); Appx7791-7794, Appx7824-7829, Appx7891-7892 (demonstratives).

In the end, the relevant standard for establishing obviousness — which was not applied by the district court here — is whether a POSA would have had a motivation to formulate a CR oxymorphone composition as claimed, and would have had a reasonable expectation, not certainty, of success. *See Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (“patentability is not imparted where the prior art would have suggested to [a POSA] that this process should be carried out and would have a reasonable likelihood of success”) (internal quotation omitted).

The answer based on the undisputed record should have been “yes.” Endo did nothing to rebut the *prima facie* case of obviousness. As discussed below, Endo’s arguments, picking on the measurement apparatus used in some of the prior art and asserting that inherent

properties of the disclosed prior art formulations added patentable subject matter, fail.

2. The broad claimed dissolution ranges are standard target for 12-hour CR formulations and within the prior art.

Endo repeatedly argued before the district court that it was the first to physically make CR oxymorphone formulations as claimed in the patents-in-suit, *e.g.* Appx448-449, Appx1928-1929, but that is of no legal relevance to the obviousness analysis at hand. *See Merck*, 874 F.2d 807-09. It is a matter of routine experimentation, not invention, for a POSA to make prior art-described CR oxymorphone formulations using the dissolution profile targets in the prior-art references disclosing similar dissolution rates for effective 12-hour CR opioids. *See* Appx20078 (noting Endo submitted declaration during prosecution stating “formulating a drug to have a desired dissolution profile is routine”); Appx3221 (Endo’s expert agreeing formulating a drug to have a desired dissolution profile is routine).

A POSA would have reasonably expected to achieve an effective CR oxymorphone formulation within the broad dissolution ranges claimed by Endo, because the broad ranges claimed are merely a general target for almost any 12-hour CR product and encompass structurally-similar prior

art CR opioid formulations' dissolution. *See* Appx1912-1913, Appx1959-1960, Appx1963-1972, Appx1975-1977, Appx2019, Appx2260-2274, Appx2291-2292, Appx7805-07, Appx7812, Appx7981, A7983. A POSA would have expected an effective dissolution profile for 12-hour CR oxymorphone would be similar to the dissolution profiles for structurally similar prior art 12-hour CR opioid formulations. Appx1882-1883, Appx1964, Appx1968, Appx2277-2278, Appx2292-2294.

The Baichwal patent, describing the prior art system supplied to Endo by its vendor Penwest, even disclosed the expected dissolution profiles based upon its testing with Albuterol. Appx7546 (Table 6), Appx7547 (Table 12); *see also* Appx1968-1970. At trial, Defendants' expert Dr. Banakar testified that the reported dissolution profile was "very typical" of the sustained release dissolution profiles he had observed over the course of his long career for most medicaments, including opioids. Appx1970.

Predictably, the dissolution rates used by Endo with oxymorphone in the Penwest controlled-release delivery system were close to the rates reported in the Baichwal patent. For example, after four hours, the prior art Baichwal patent had reported dissolution of 60.3, 61.4, 63.9 and 65.1 in

Tables 6 and 12. Appx7546-7547. Endo reported similar dissolution statistics (58.1, 66.3 and 66.9) in its Table 4. Appx283. Both sets of data fell well within the expansive range actually claimed by Endo of between 45 and 80%. There was no dispute over measurement procedures with respect to data reported in the Baichwal patent—because the dissolution profiles were measured by the exact same 50 rpm Paddle Method identified in the ‘122 and ‘216 patents. Appx1968, Appx7546. The district court simply ignored this data.

Maloney too disclosed dissolution profiles with an opioid analgesic that fell within those claimed in the ‘122 and ‘216 patents. Appx1959-1960, Appx1975-1977, Appx7614, Appx7805-7806. So did prior art showing the dissolution profiles of structurally-similar CR opioid morphine and oxycodone products. Appx2260-2274, Appx2291-2292, Appx7981, A7983.

Moreover, Oshlack teaches, and in fact has issued claims covering, precisely what Endo falsely argued to the PTO during prosecution of its patents was lacking in the art: a target dissolution profile for CR oxymorphone effective for at least 12 hours. Appx7554-7620, *e.g.* at Appx7587 (claims 1, 10-11); *see also* Appx1937, Appx1958, Appx1965-1968, Appx2019; *cf.* Appx20077-20078 (Endo arguing prior art does not disclose

“any guidance for achieving an analgesically effective oxymorphone controlled release dosage form” such as a “release rate” or “desired dissolution profile”). Not crediting these disclosures was error. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1374-76 (Fed. Cir. 2005) (district court clearly erred in finding significant differences between claimed invention and prior art and misinterpreting scope and content of prior art).

3. Asserted claims’ reference to paddle method of dissolution measurement cannot save claims from invalidity.

Rather than crediting the overwhelming evidence that showed that the claimed dissolution ranges were standard and were disclosed in numerous pieces of prior art discussed above using both USP-approved measurement techniques (Paddle and Basket), the district court imposed an incorrect burden on Defendants. The district court erred as a matter of law by holding it was incumbent on Defendants to prove “interchangeability” and a specific numerical “correlation” “equat[ing] the results” of the previously disclosed dissolution results with the claimed ranges in the patents measured using the USP paddle dissolution testing method.

As this Court previously stated:

[I]t makes no difference, a priori, to the question of obviousness whether the hypothetical person of ordinary skill in the art

would have understood the claimed dissolution profile in terms of a Paddle-Method or a Basket-Method test range, just as it would make no difference whether the hypothetical person of skill in the art preferred to think in English or Metric units. The claimed subject matter is not presumed to change as a function of how one elects to measure it.

Kao, 639 F.3d at 1066. The district court never heeded this guidance and imposed a standard that would effectively allow applicants to obtain patents by simply measuring parameters in a way that was different than previously reported.

The fact that the dissolution rates in the asserted claims were measured by one method and the dissolution rates in some prior art (*e.g.* Oshlack, Maloney) were measured using an alternate approved USP method is of no moment. The Court recognized this in *Kao* when it noted that “subject matter is not presumed to change as a function of how one elects to measure it” and on remand the Board should consider “the importance, or *lack thereof*, of the claimed range to the alleged nonobviousness of the invention.” 639 F.3d at 1066, 1067 (emphasis added).

Moreover, the district court failed to recognize that, as a matter of law, subject matter claimed in prior art patents like Oshlack are *presumed* enabled. “[P]rior art patents are presumed enabled,” and thus patentees

bear the burden to rebut that presumption. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354-55 (Fed. Cir. 2003) (holding that the court erred in requiring accused infringer to prove enablement of prior art).

Because Oshlack claims the same subject matter as the asserted claims – CR oxymorphone formulations effective over at least 12 hours – the fact it recites an alternate dissolution method is presumed to not prevent a POSA from achieving that subject matter and Endo must rebut that presumption.

Thus, it was legal error for the district court to require Defendants to prove that “the results of the dissolution testing methods used in the prior art could be read to indicate the results of the dissolution testing methods” reciting an alternate measurement test. Appx100. The prior art subject matter is presumed enabled as a matter of law, and “the claimed subject matter is not presumed to change as a function of how one elects to measure it.” *Kao*, 639 F.3d at 1066.

However, even if evidence of a relationship between alternately-measured dissolution profiles is required, that evidence was supplied at trial. Defendants presented evidence based on Madden and the Dissolution Handbook prior art that the USP Paddle method at 50 rpm (recited in most asserted claims) and USP Basket method at 100 rpm (identified in, *e.g.*,

Oshlack & Maloney) are considered to produce roughly equivalent dissolution results, particularly in the context of CR formulations like at issue here. Appx1972-1980, Appx2007-2008, Appx6429 (Madden), Appx7494 (Handbook); *see also* Appx104 (district court noting Madden prior art in discussing release of highly soluble drugs (like oxymorphone) from a hydrophilic matrix tablet (like claimed CR formulations) found such CR formulations “produce similar dissolution profiles” “regardless of the degree of agitation” or apparatus (paddle or basket) used).

No more specific formula, correlation or calculation is required. Although the district court credited Endo’s evidence that there was no specific numerical correlation between measurements obtained via the alternate measurement techniques, Appx104-107, *Kao* never required such evidence in the first place. *Kao* merely held that the Board’s particular reasoning lacked adequate factual support because it relied on an unsupported specific numerical correlation. 639 F.3d at 1066-67.

Even if the basket method at 100 rpm and the paddle method at 50 rpm do not always result in precisely equivalent data or have an established specific numerical correlation – the most that Endo’s evidence may suggest – the only reasonable conclusion from all the record evidence

is that the dissolution ranges taught by prior art for 12-hour CR oxymorphone, *e.g.* Oshlack, Baichwal or Webster, at a minimum overlap⁸ the ranges in the '122 and '216 patents.⁹ The district court did not make a specific finding to the contrary (and to the extent it implicitly made one, it was clear error). For the dissolution ranges in the asserted claims to fall outside those ranges disclosed in Oshlack, the basket method at 100 rpm would have to exhibit dissolution greater than two times the rate exhibited by the paddle method at 50 rpm.¹⁰ There was no evidence whatsoever

⁸ “For a prior-art reference to be enabling, it need not enable the claim in its entirety, but instead the reference need only enable a single embodiment of the claim.” *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015) (citing *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003)). “It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is ‘anticipated’ if one of them is in the prior art.” *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 778 (Fed. Cir. 1985) (citing *In re Petering*, 301 F.2d 676, 682 (C.C.P.A. 1962)).

⁹ The USP Basket (100 rpm) and USP Paddle (50 rpm) methods are just different ways of agitating a tablet in solution both meant to simulate the dissolution effect of the GI tract. Appx1909-1911. Some of the presented prior art teaching an overlapping dissolution profile for structurally-similar 12-hour CR opioids, like the claims-in-suit, measured dissolution by the paddle method at 50 rpm. *See* Appx2262-63 (discussing the Webster prior art), Appx7975; *see also supra* p. 46 (discussing Baichwal).

¹⁰ 42.5%, the highest release claimed by Oshlack at 1 hour, is more than 2 times the 15% lower limitation for release at 1 hour recited in the '122 and

adduced at trial that could support a finding of any difference of this magnitude, and the district court made no such finding. To the contrary, it acknowledged that the two measurement techniques could be “roughly equivalent in producing dissolution.” Appx106; *see also* Appx104 (acknowledging Madden’s findings regarding similar production of dissolution in specific context of similar CR formulations).

This Court has “consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness” and “also held that a *prima facie* case of obviousness exists when the claimed range and the prior art range *do not overlap* but are close enough such that one skilled in the art would have expected them to have the same properties.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (citations omitted) (emphasis added). A POSA would have every expectation that an oxymorphone formulation exhibiting a dissolution rate measured by the method claimed by Oshlack would have the same 12-hour “effective” properties Endo claimed in the patents-in-suit. That would be the reasonable expectation because (i) that is exactly what Oshlack had already claimed could be achieved, Appx1965-

‘216 claims. 90%, the highest release disclosed by Oshlack at 4 hours, is exactly 2 times the 45% lower limitation for release at 4 hours recited in the ‘122 and ‘216 claims. Appx7587; *cf.* Appx291-291, Appx320-324.

1968, Appx2019,¹¹ and (ii) the fact that structurally-similar opioid formulations exhibiting dissolution properties within the same ranges were known to be effective. *Id.*; *see also* Appx1913, Appx1970, Appx2170, Appx2259-2274.

The evidence of record establishes that a CR oxymorphone formulation having dissolution properties measured by either the paddle method at 50 rpm or the basket method at 100 rpm would be expected to produce roughly, or functionally, equivalent results in the types of CR formulations at issue. Appx1964-1980, Appx3363-3371, Appx6429.¹² Even

¹¹ *See Kao*, 639 F.3d at 1066 (“the claimed subject matter is not presumed to change as a function of how one elects to measure it”).

¹² Although the Court referenced statements from two prior-art references (Shargel, Hardwidge) indicating that different methods could produce “different” measurement results or that there is “no simple correlation,” *i.e.*, no specific numerical or mathematical correlation, that holds true across every type of conceivable formulation, Appx104-05, none of the prior art taught that the measurement results would be *functionally* or *substantially* different in the context of CR formulations like the ones at issue in this case. Indeed, even the complete Shargel and Hardwidge references cited by the district court indicated the contrary. Appx3368-3371 (Endo’s expert acknowledged the Hardwidge reference concludes “large differences would not be anticipated” and different measurements “correlated well with each other” in general functional sense); Appx6079 (Banaker article citing Hardwidge and making similar conclusion), Appx6087-6090 (Hardwidge), Appx6159-6160 (Shargel reference recognizes that “[d]issolution results at 50 rpm with the paddle method may be

Endo admitted that the dissolution of CR oxymorphone tablets are “unaffected by” and “insensitive to hydrodynamic agitation [stirring rate or rotation speed and] dissolution apparatus.” Appx3378-3380, Appx37114, Appx37171; *see also* Appx1978-1980, Appx6986-7029, Appx7817-7820.

The many similar dissolution profiles disclosed in the prior art, even when using an alternate approved measurement method (*e.g.* Oshlack, Maloney), renders obvious – the asserted claims. Endo’s strategy of highlighting the alternate measurement technique in some prior art references cannot change the fact that the prior art as a whole disclosed and motivated a POSA with a reasonable expectation of success to make the same subject matter.

C. The district court erred in giving patentable weight to functional pharmacokinetic limitations inherent to the formulations disclosed by the prior art.

The district court erred as a matter of law to the extent it failed to find the asserted claims obvious because of any of the pharmacokinetic claim limitations. The district court acknowledged that the claimed pharmacokinetic limitations naturally occur as “the result of the body’s

equivalent to the dissolution at 100 rpm with the basket method”), Appx3365 (Endo’s expert acknowledging same); Appx1978-1979.

natural processes” following administration of an effective CR oxymorphone formulation. Appx111; *see also* Appx1914 (“Pharmacokinetics ... is all biologically controlled.”), Appx1923 (“pharmacokinetic results ... are due to natural processes of the body acting on the drug from the tablet”). Nonetheless, because the district court believed (wrongly) that CR oxymorphone was not taught by the prior art it found that the pharmacokinetic limitations should be afforded patentable weight. *See* Appx107-119, *e.g.* at Appx111 (“These pharmacokinetic effects *are only possible* because the dosage form, the invention itself, slows the release of oxymorphone ...”).

But as detailed above, a CR oxymorphone dosage form, in-and-of-itself, according to this Court’s binding precedent, was not inventive. *See Kao*, 639 F.3d at 1070 (“Maloney’s express teachings render the claimed controlled release oxymorphone formulation obvious”). “Substantial evidence supports the Board’s finding ...that the claimed ‘food effect’ is an inherent property of oxymorphone” *Id.* at 1070. The food effect and other pharmacokinetic limitations thus add “nothing of patentable consequence” to the asserted claims that can save them from invalidity over the prior art. *Id.*

As a matter of law, functional pharmacokinetic limitations resulting from the administration of a pharmaceutical formulation, cannot lend patentable weight to the claims. “It is not invention to perceive that the product which others had discovered had qualities they failed to detect.” *Kubin*, 561 F.3d at 1357 (quoting *Gen. Elec.*, 326 U.S. at 249).

Defendants met their burden of proof to establish the fact that the prior art disclosed CR oxymorphone formulations effective for at least 12 hours for administration to patients. *See, e.g.*, Appx1891-1903, Appx1911-1913, Appx1958-1971, Appx2260-2274, Appx7792, Appx7554-7590 (Oshlack), *e.g.* at 1:42-53, 3:54-57, 4:8-10, 4:64-5:4, 5:25-31, 11:65-12:11, 19:5-12, 25:49-54, 26:34-38; Appx7535-7553 (Baichwal); Appx7591-7620 (Maloney); *see also Kao*, 639 F.3d at 1071 (“the oxymorphone formulation disclosed in Maloney would satisfy the claimed 12-hour limitation”); *see also supra* pp. 18-22. Defendants did not need to present any additional evidence in regard to the pharmacokinetic limitations as they are merely inherent properties of the prior art formulations resulting from administration. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (“blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious

formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations”); *King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1274-76 (Fed. Cir. 2010) (rejecting argument that defendant did not provide sufficient evidence “that the prior art would necessarily result in” claimed effect from administration of drug with food because prior art disclosed administering drug with food and even subject patent’s intrinsic evidence indicated disputed claim limitation was merely functional effect of administering the drug with food); *see also* Appx712, Appx714-716 (Endo’s inventor conceding at trial food effect, conversion of oxymorphone in part to its metabolite 6-OH oxymorphone, and multiple peaks (pharmacokinetic limitations in asserted claims) are merely inherent properties resulting from how body processes oxymorphone); Appx1990-2002, Appx2008-2018 (expert explaining how claimed pharmacokinetic limitations are merely natural result of how body acts on oxymorphone).

In short, the pharmacokinetic limitations recited in the asserted claims, even if previously unappreciated by a POSA, cannot save the claims from invalidity because reciting a function of a known structure does not impart “patentable weight” to claims. *In re Schreiber*, 128 F.3d

1473, 1477 (Fed. Cir. 1997); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349-50 (Fed. Cir. 2002) (“Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art.”) (quotations omitted); *Abbott Labs. v. Baxter Pharm. Prods.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006) (“The general principle that a newly-discovered property of the prior art cannot support a patent on that same art is not avoided if the patentee explicitly claims that property.”); *Santarus*, 694 F.3d at 1354.

The pharmacokinetic properties recited in the asserted claims naturally flow from the administration of a 12-hour CR oxymorphone formulation. Thus, those recited properties cannot differentiate the CR oxymorphone formulations of the asserted claims from the CR oxymorphone formulations taught by the prior art, *e.g.*, Oshlack or Maloney, or Baichwal and Penwest.

D. The district court erred by not requiring evidence of a nexus between any alleged objective indicia of non-obviousness and an aspect of the claims not found in the prior art.

The district court also ignored the legal directive that a patentee, when making arguments concerning the objective indicia of non-

obviousness, *must* establish a nexus between that evidence and the merits of, *i.e.* a novel feature of, the claimed invention in order for the objective indicia, or secondary considerations, to be accorded weight. *Kao*, 639 F.3d at 1068 (citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011)); *see also id.* at 1069-70 (“if the same behavior would be observed in any oxymorphone controlled release formulation, then there is no necessary nexus”). The district court credited Endo’s evidence of secondary considerations based on the “commercial success” of Opana® ER, which it attributed to its 12-hour dosing interval and analgesic effectiveness, as well as the long-felt but unmet need for additional CR opioids. Appx119-122. But those are aspects of any 12-hour effective CR oxymorphone formulation, which this Court already recognized are insufficient to show a nexus to anything novel given the teachings of the prior art. *Kao*, 639 F.3d at 1068-70; *see also id.* at 1071 (“the oxymorphone formulation disclosed in Maloney would satisfy the claimed 12-hour effectiveness limitation”), 1073 (“the administration of controlled release oxymorphone is squarely present in the prior art”). Thus Endo presented no relevant evidence of secondary

considerations, and certainly none that could overcome Defendants' powerful evidence of obviousness.

II. Endo's Patent Claims Are Invalid for Failing to Meet the Requirements of 35 U.S.C. § 112.

A. The district court erred as a matter of law by not requiring the written description of the patents to show the inventors possessed the full scope of the claims.

All of the asserted claims recite limitations requiring an analgesically-effective dose for at least 12 hours or dissolution ranges allegedly corresponding to said "effective" dosage. The claimed dissolution ranges encompass thousands of different formulations. But the specification discloses only three formulations that fall within a much narrower dissolution range than the ones claimed. *See* Appx264-324, *e.g.* at 10:42-63 (specification disclosing dissolution 27.8-32.3% at one hour, 58.1-66.9% at four hours, and 85.3-95.8% at ten hours), '122 claims 1-3, 19 (claiming dissolution of 15-50% after one hour, 45-80% after four hours, and more than 80% after ten hours); *see also* Appx2307-2310, Appx2315-2318.

Moreover, Endo only tested *one* formulation, its commercial formulation, in any clinical trials relating to efficacy. And the shared patent specification does not even disclose what formulation (or specific

dissolution profile) was tested for “efficacy” nor does it disclose the methodology or specific studies used to support “efficacy.” *See* Appx749, Appx3182-3189, Appx3382-3384, Appx3388. The patent obscures the fact that the only efficacy-related testing obliquely referenced in 2 figures in the patent specification does not come from any study directly testing efficacy of any formulation in a controlled manner, but rather from comparing results of two different studies in a non-standard way that would not establish efficacy by industry standards. *See id.*; Appx797-808.

Although the written description inquiry is a question of fact reviewed for clear error, the district court’s application of an incorrect legal standard is reviewed *de novo*. *See Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). In order for claims to be valid, the patent must contain a written description that shows that the inventors had possession of *the full scope* of the claimed subject matter. *See* 35 U.S.C. § 112; *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The district court did not require that the ‘122 or ‘216 patent disclose the full scope of the claims, but rather held that Endo could have claims broader

than or “encompassing” the disclosed invention so as to not invite infringement or design-around. Appx128.

The district court erred as a matter of law because the inventors here are not entitled to claims broader than what was in their possession at the time of their purported invention. This is particularly the case when “functional language” is used to “define the boundaries of a claimed genus” —like here where Endo has essentially sought a monopoly on any effective CR oxymorphone formulation by reciting broad dissolution ranges within which any effective CR oxymorphone formulation would obviously fall somewhere. “[T]he specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.” *Ariad*, 598 F.3d at 1349 (emphasis added). “[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.” *Id.*

Endo argued its purported invention was not “ready for patenting” until after it completed a clinical study showing the analgesic effectiveness

of its commercial formulation over 12 hours. The district court adopted Endo's argument when addressing Defendants' on-sale bar defense. Appx123-125. But the commercial formulation is merely one species of Endo's claims, which covers the genus of all "effective" CR oxymorphone formulations. And the patent specification does not even disclose industry-standard efficacy testing for that one formulation.

Furthermore, Dr. Lee, the only inventor to testify at trial, testified unequivocally that the inventors were not in possession of effective formulations having dissolution rates throughout the broadly claimed ranges because they had *no idea* if formulations with dissolution rates falling toward the low or high end of the claimed ranges would be effective. Appx719-720. Endo then argued, and the district court found significant, that the Defendants in subsequently seeking to market generic versions of CR oxymorphone, produced certain dissolution results almost throughout the broad dissolution ranges of Endo's claims. Appx2349-2355, Appx3358-3359, Appx128.

Because a patent is "not a reward for the search, but compensation for its successful conclusion," the "written description requirement prohibits a patentee from 'leaving it to the industry to complete an

unfinished invention.” *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013) (citation omitted). One cannot functionally claim everything that achieves a useful result without defining exactly what compounds achieve that result, and then leave it to the pharmaceutical industry to complete the invention by determining additional species meeting the result. *See Ariad*, 598 F.3d at 1353.¹³ Because the asserted claims far exceed what even the inventors at the trial explicitly acknowledged was the invention they possessed, the claims are invalid for lack of written description. *See Novozymes*, 723 F.3d at 1350. Written description ensures that “the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him.” *Chiron*, 363 F.3d at 1255.

¹³ The district court’s legal error in failing to apply the correct law regarding the written description requirement is highlighted by the Court’s response to an objection made by defense counsel to Endo presenting, during its expert’s rebuttal to defendants’ written description case, testimony regarding dissolution testing of defendants’ products done years after the filing date of the application for the patents-in-suit. Defense counsel objected on relevance grounds, noting “[w]hat is done 15 or ten years later by the defendants does not bear on written descriptions by the plaintiffs in their specifications.” The district court responded: “I disagree. Overruled.” Appx3358.

As detailed in section I above, the asserted claims are obvious, because even based on prior art like Oshlack, Maloney, or Baichwal and Penwest, a POSA would have been motivated to, with a reasonable expectation of success, formulate an effective (for 12 hours) CR oxymorphone formulation. Indeed, the PTO previously found Oshlack to be enabling of such formulation when it issued Oshlack's claims. *See also Kao*, 639 F.3d at 1071 ("Although Endo's experts stated their view that Maloney did not enable the disclosed oxymorphone formulation, their statements were based on various 'concerns' that fall short of establishing that the Maloney reference was non-enabling.").

If the prior art is non-enabling because the field is so unpredictable that one cannot truly ever know if a formulation is likely to be effective until full clinical studies have been conducted and the results "carefully scrutinized and memorialized" as Endo argued at trial, *see* Appx124, Appx3247-3249, then Endo did not possess the full scope of its own claims as it presented in the specification of the patents-in-suit no clinical, or other, data showing the effectiveness of tablets at either end of its claimed dissolution ranges. *See* Appx2318-2320, Appx2338, Appx3188-3189. When "the invention described in [an] application is of a much narrower scope

than the invention ultimately claimed in the [] patent,” the claims are invalid for lack of an adequate written description. *Chiron*, 363 F.3d at 1259.

B. The multiple peaks claims are invalid for indefiniteness.

Asserted claims 1, 71, and 78 of the ‘216 patent are also invalid on the basis that the term “peaks” is indefinite. *See* Appx321-324 at claim 1 (“the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration”), claim 66 upon which claim 71 depends (“the blood plasma levels of oxymorphone comprise one or more peaks”), claim 78 (“the blood plasma level of oxymorphone displays two or three peaks over about the first 12 hours after administration”). A claim is indefinite if it fails to “inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). Indefiniteness is a question of law reviewed by this Court *de novo*. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). “The internal coherence and context assessment of the patent, and whether it conveys claim meaning with reasonable certainty, are questions of law.” *Id.* at 1342. “There is an indefiniteness problem if the claim language might mean several different things and no informed and confident choice is available among the

contending definitions.” *Interval Licensing LLC v. AOL Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014) (internal quotation marks and citation omitted).

The district court construed a “peak” as “where blood concentration reaches a high-point before declining,” and dismissed any dispute about the meaning of “peaks” as academic. Appx29-30. It also rejected Defendants’ indefiniteness argument stating, “[T]he definition of the term ‘peak’ would be readily apparent to a [POSA] upon reading the specification.” Appx126.

But the district court’s own construction highlights the indefiniteness of these claims. If a peak in blood concentration is “a high-point before declining,” the claims’ reference to more than one “high-point” is nonsensical. The district court’s discussion indicates perhaps that it meant “a high-point before declining” on a “curve.” See Appx29. But to a POSA this just begs the question of what exactly qualifies as a “curve,” e.g., as opposed to a shoulder or a plateau. See Appx1997, Appx2221-2224.

In disputing the invalidity of the claims and arguing for their issuance, Endo asserted that prior-art immediate-release formulations of oxymorphone did not have multiple “peaks.” Endo argued that such multiple “peaks” are not inherent to oxymorphone itself (in order to imply

it was also not inherent to CR oxymorphone formulations taught by prior art). *See Kao*, 639 F.3d 1068 (noting Endo argued “unlike immediate release formulations ... [its] controlled-release formulation resulted in unexpected multiple peaks”). However, at trial, the ‘216 patent inventor acknowledged multiple peaks resulted from prior-art IR formulations and was not an inventive feature of the ‘122 and ‘216 patents. Appx715-716.¹⁴ The only way Endo’s prosecution argument could have made any sense is if a “peak” as used in the patent had some special meaning representing a level of some particular sufficient magnitude such that “rises” or “high-points” in plasma levels that would exist in prior art IR or CR oxymorphone formulations do not constitute “peaks” but those in its CR oxymorphone formulations do because of their significantly higher magnitude.

Yet the patents-in-suit contain no explanation of how a “peak” should be measured or what level of change (rise/dip) or “curve” in measurements constitutes a “peak.” Therefore, if the “multiple peaks”

¹⁴ Multiple Endo documents also contradict Endo’s statements made during prosecution and show Endo knows multiple peaks result from oxymorphone administration, regardless of the type of formulation it is in, and this inherent property is not unexpected given other opioids also exhibit multiple peaks. *See* Appx1998-2002, Appx2009-2012, Appx7865 (“Multiple peaks are ... observed for both solution and CR formulations, which is consistent with other opioids.”), Appx7866, Appx7870.

claims are not already invalid for obviousness or insufficient written description, they are invalid for indefiniteness.

III. Defendants' ANDA Products Do Not Infringe the "Food Effect" Claims.

To the extent Endo disputes that the food effect limitations are inherent properties of the prior art as this Court recognized in *Kao*, 639 F.3d at 1070, then the judgment of infringement of the claims with those limitations cannot stand. The "food effect limitations" in the asserted claims come in two varieties that require the existence of certain ratios between measurements under fed (full stomach) and fasted (empty stomach) conditions. Appx1126. The first limitation requires that C_{\max} (maximum concentration of drug) be at least 50% higher in fed patients than in fasted patients. Appx1131, Appx322-324 (see claims 40, 42, 50, 54, 77, 78, 79, 80, 82). The second limitation requires that the AUC (area under the curve) measurement be less than 20% higher under fed versus fasted conditions. Appx1131, Appx292 (see claim 20), Appx322-324 (see claims 40, 50, 54, 77, 78, 79, 80, 82).¹⁵

¹⁵ Claims 40 and 42 of the '216 patent were found non-infringed for other reasons and need only be addressed if this Court reverses the non-infringement finding below as requested by Endo's noticed cross-appeal.

If the claimed food effects are not inherent to all CR oxymorphone formulations, then Endo put forth no competent evidence to show Defendants' products would infringe. Endo's expert candidly admitted that he did not compare the asserted claims and Defendants' accused products. Appx1133 ("I did not"); *see also* Appx1138, Appx1143-1144, Appx1159. Endo's expert (Dr. Fassihi) did not examine *any* data concerning Defendants' products under fed and fasted conditions to determine infringement. He readily admitted that he could have performed – but chose not to perform – relevant studies and conduct the proper infringement analysis. Appx1132. Dr. Fassihi also chose not to rely on data concerning fed and fasted measurements that Defendants had provided in their ANDAs. He testified that he chose not to rely on that data because the studies (while properly done for bioequivalency purposes) did not constitute "proper" food-effect studies. Appx1147-1149; *see also* Appx1157-1159.

Dr. Fassihi instead embarked on an unreliable series of inferences starting with an analysis of Endo's products. Appx1143. First, Dr. Fassihi theorized that because Defendants had claimed that their products were bioequivalent to the reference drug ("RLD") identified in their respective

ANDAs,¹⁶ he could assume that if the RLD met the food effect claim limitations then Defendants' products would as well. Appx1142. But that assumption has two flaws: (1) with respect to products that used Endo's original formulation as the RLD, Dr. Fassihi had readily agreed that the bioequivalence studies were not proper food effect studies; and (2) there was no food effect data or studies available for the reformulated reference drug. Appx1139, Appx1141.

Because there was no fed/fasted study relating to Endo's current reformulated product, Dr. Fassihi made a second level of unsupported inferences and relied upon data from fed/fasted studies relating to Endo's initial product (which had since been withdrawn from the market).

Appx1142. But the claimed bioequivalence between Endo's original formulation and its reformulated RLD would not mean that the C_{\max} or AUC results would be the same for both formulations. In fact, Dr. Fassihi testified that the relevant measurements for the original formulation may very well be different for the reformulated product. Appx1145-1146.

¹⁶ Certain of the Defendants filed ANDAs identifying Endo's original oxymorphone CR formulation as the RLD, while other defendants filed ANDAs identifying Endo's reformulated oxymorphone CR product as the RLD. See Appx14.

Dr. Fassihi also testified that the results from the decade-old fed/fasted data from a prior version of Opana® ER may be different from the data yielded from actual tests of Defendants' products (had such tests been conducted). Appx1145–1147. Those data differences could be significant because FDA bioequivalence allows for significant variations (roughly allowing the generic value to vary between 80 and 125% of the reference value) and variations in multiple measurements can multiply the amount of error when, as here, a comparison of those measurements is required by the claims. For example, Dr. Fassihi testified that Defendants' products could have a lower C_{\max} in the fed state and a higher C_{\max} in the fasted state than Opana® ER, Appx1147, which would reduce the difference between C_{\max} in the fed versus fasted state bringing the percentage difference outside the scope of the claims.¹⁷ Thus Endo's evidence was insufficient as a matter of law. *See Adams Respiratory Therapeutics, Inc. v. Perrigo, Inc.*, 616 F.3d 1283, 1289 (Fed. Cir. 2010)

¹⁷ Dr. Fassihi also relied upon Defendants' package inserts to support his opinion. Appx1133. He admitted, however, that those inserts merely reported the information that Endo supplied regarding its original product and did not reflect any studies that actually measured fed/fasted statistics for any of Defendants' products. Appx1161–1162.

(reliance “on the mere fact of bioequivalence of the two sets of products ... would not be enough to survive summary judgment”).

Without doing an actual analysis of Defendants’ products and comparing those results to the requirements of the asserted claims, Endo did not meet its burden to prove infringement. The judgment of infringement of the “food effect” claims cannot stand.

Conclusion

The judgments of the district court should be reversed. All asserted ‘122 and ‘216 patent claims should be held invalid and not infringed. The injunctive relief granted to Endo should be vacated.

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ADDENDUM

Start No.	End No.	Description
Judgment, Order or Decisions in Question (and supporting opinions, memorandums, or findings and conclusions)		
Appx1	Appx159	Findings of Fact and Conclusions of Law, dated August 14, 2015 [Docket No 218 in Case No. 12 Civ. 8060 (SDNY) (unredacted version); Docket No. 220 in Case No. 12 Civ. 8060 (SDNY); Docket No. 148 in Case No. 12 Civ. 8115 (SDNY); Docket No. 154 in Case No. 12 Civ. 8317 (SDNY); Docket No. 107 in Case No. 12 Civ. 8985 (SDNY); Docket No. 135 in Case No. 13 Civ. 0435 (SDNY); Docket No. 141 in Case No. 13 Civ. 0436 (SDNY); Docket No. 194 in Case No. 13 Civ. 3288 (SDNY); Docket No. 105 in Case No. 13 Civ. 4343 (SDNY); Docket No. 96 in Case No. 13 Civ. 8597 (SDNY) (public redacted versions)]
Appx160	Appx163	Judgment, filed August 24, 2015 [Docket No. 225 in Case No. 12 Civ. 8060 (SDNY); No. 149 in Case No. 12 Civ. 8115; Docket No. 155 in Case No. 12 Civ. 8317 (SDNY); Docket No. 108 in Case No. 12 Civ. 8985 (SDNY); Docket No. 136 in Case No. 13 Civ. 0435 (SDNY); Docket No. 142 in Case No. 13 Civ. 0436 (SDNY); Docket No. 195 in Case No. 13 Civ. 3288 (SDNY); Docket No. 106 in Case No. 13 Civ. 4343 (SDNY); Docket No. 97 in Case No. 13 Civ. 8597 (SDNY)]
Appx164	Appx192	Order (Omnibus Opinion) of the Honorable Thomas P. Griesa, filed April 29, 2016 [Docket No. 255 in Case No. 12 Civ. 8060 (SDNY); Docket No. 170 in Case No. 12 Civ. 8115 (SDNY); Docket No. 183 in Case No. 12 Civ. 8317 (SDNY); Docket No. 156 in Case No. 12 Civ. 8985 (SDNY); Docket No. 164 in Case No. 13 Civ. 0435 (SDNY); Docket No. 173 in Case No. 13 Civ. 0436 (SDNY); Docket No. 227 in Case No. 13 Civ. 3288 (SDNY); Docket No.

		130 in Case No. 13 Civ. 4343 (SDNY); Docket No. 122 in Case No. 13 Civ. 8597 (SDNY)]
Appx8321	Appx8324	Order dated August 14, 2015 [Docket No. 219 in Case No. 12 Civ. 8060 (SDNY); Docket No. 147 in Case No. 12 Civ. 8115 (SDNY); Docket No. 153 in Case No. 12 Civ. 8317 (SDNY); Docket No. 134 in Case No. 13 Civ. 0435 (SDNY); Docket No. 140 in Case No. 13 Civ. 0436 (SDNY); Docket No. 193 in Case No. 13 Civ. 3288 (SDNY); Docket No. 104 in Case No. 13 Civ. 4343 (SDNY); Docket No. 95 in Case No. 13 Civ. 8597 (SDNY)]
Appx8513	Appx8515	Amended Judgment, filed June 29, 2016 [Docket No. 180 in Case No. 12 Civ. 8115 (SDNY)]
Appx8516	Appx8519	Amended Judgment, filed June 29, 2016 [Docket No. 193 in Case No. 12 Civ. 8317 (SDNY)]
Appx8520	Appx8523	Amended Judgment, filed June 29, 2016 [Docket No. 174 in Case No. 13 Civ. 0435 (SDNY)]
Appx8528	Appx8530	Amended Judgment, filed June 29, 2016 [Docket No. 235 in Case No. 13 Civ. 3288 (SDNY)]
Appx8531	Appx8533	Amended Judgment, filed June 29, 2016 [Docket No. 140 in Case No. 13 Civ. 4343 (SDNY)]
Appx8534	Appx8536	Amended Judgment, filed June 29, 2016 [Docket No. 132 in Case No. 13 Civ. 8597 (SDNY)]
Appx8537	Appx8542	Order Resolving Post-Trial Motions, filed June 29, 2016 [Docket No. 264 in Case No. 12 Civ. 8060 (SDNY); Docket No. 179 in Case No. 12 Civ. 8115 (SDNY); Docket No. 192 in Case No. 12 Civ. 8317 (SDNY); Docket No. 131 in Case No. 12 Civ. 8985 (SDNY); Docket No. 173 in Case No. 13 Civ. 0435 (SDNY); Docket No. 182 in Case No. 13 Civ. 0436 (SDNY); Docket No. 234 in Case No. 13 Civ. 3288 (SDNY); Docket No. 139 in Case No. 13 Civ. 4343 (SDNY); Docket No. 131 in Case No. 13 Civ. 8597 (SDNY)]

Patents-in-Suit		
Appx264	Appx292	U.S. Patent No. 8,309,122
Appx293	Appx324	U.S. Patent No. 8,329,216

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

-----	x	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	12 Civ. 8115 (TPG)
	:	
AMNEAL PHARMACEUTICALS, LLC and	:	
AMNEAL PHARMACEUTICALS OF NEW	:	
YORK, LLC	:	
	:	
Defendants.	:	
-----	x	

	:	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	12 Civ. 8060 (TPG)
	:	
TEVA PHARMACEUTICALS USA, INC. and	:	
BARR LABORATORIES, INC.	:	
	:	
Defendant.	:	
-----	x	

	:	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	12 Civ. 8317 (TPG)
	:	
IMPAX LABORATORIES, INC. and THORX	:	
LABORATORIES, INC.	:	
	:	
Defendants.	:	
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*(captions continued on
following pages)*

FINDINGS OF FACT AND CONCLUSIONS OF LAW

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ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	
	:	12 Civ. 8985 (TPG)
ACTAVIS INC. and ACTAVIS SOUTH	:	
ATLANTIC LLC,	:	
	:	
Defendants.	:	
-----	x	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	13 Civ. 435 (TPG)
	:	
IMPAX LABORATORIES, INC.,	:	
	:	
Defendants.	:	
-----	x	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	
	:	13 Civ. 436 (TPG)
ACTAVIS INC, ACTAVIS SOUTH	:	
ATLANTIC LLC, and WATSON	:	
PHARMACEUTICALS, INC.,	:	
	:	
Defendants.	:	
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ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13 Civ. 3288 (TPG)
	:	
ROXANE LABORATORIES, INC.,	:	
	:	
Defendant.	:	
-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13 Civ. 4343 (TPG)
	:	13 Civ. 8597 (TPG)
SUN PHARMACEUTICAL INDUSTRIES,	:	
LTD.	:	
	:	
Defendant.	:	
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April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement. Plaintiffs Endo Pharmaceuticals Inc. (“Endo”) and Grünenthal GmbH (Grünenthal) argue that defendants, all of which are generic drug manufacturers, infringe on patents covering Endo’s branded painkiller OPANA®ER by selling or seeking approval to sell generic versions of the drug in either crushable or non-crushable formulations. Defendants argue that their generic products, as described in their Abbreviated New Drug Applications (“ANDAs”), do not and will not infringe the patents-in-suit, and that in any event those patents are invalid. Defendants also asserted other statutory and equitable defenses.

There are seven groups of defendants in these cases. Plaintiffs sued the defendants separately, but the cases were tried jointly upon mutual consent. The defendants are: Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively, “Amneal”); Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc. (collectively, “Teva”); Impax Laboratories, Inc. (“Impax”), ThoRx Laboratories, Inc. (“ThoRx”) Actavis Inc., Actavis South Atlantic LLC, and Watson Pharmaceuticals, Inc. (collectively, “Actavis”); Roxane Laboratories, Inc. (“Roxane”) and Sun Pharmaceutical Industries (“Sun Pharma.”).

There are three patents-in-suit. Endo owns two of the patents, United States patent numbers 8,309,122 (“the ’122 Patent”) and 8,329,216 (“the ’216 Patent”). These patents recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing. Grünenthal owns the third patent, United States Patent Number 8,309,060 (“the ’060 Patent”), which

describes an invention for drug-tablets so hard that they are difficult to abuse through crushing and snorting, and which also accommodate other barriers to abuse.

The court concludes that defendants' generic products infringe or will infringe all but two of the asserted claims of the '122 and '216 patents, and that defendants have failed to satisfy their burden of showing those claims to be invalid. Because each of the defendants infringe the asserted claims of the '122 and '216 Patents, the court enters judgment in Endo's favor and enjoins defendants from selling the generic oxymorphone products described in their ANDAs. With regard to the '060 Patent, the court finds that certain defendants infringe each of the asserted claims, but concludes that defendants have satisfied their burden of showing those claims to be obvious in light of the prior art at the time of the invention. Thus, the asserted claims of the '060 Patent are invalid.

Background Findings of Fact

Endo Pharmaceuticals Inc. was founded in 1997 as a "spinout" from the well-known DuPont Merck Pharmaceutical Company. Trial Tr. at 23:3–5. As a new drug company, Endo had considerable flexibility in deciding which new drug products to develop. *See id.* at 25–27. A number of potential projects were under consideration, including a project to explore developing a certain opioid, oxymorphone, into a controlled-release tablet. *See generally* Project Team Minutes (Feb. 12, 1998) (PTX-0157). Oxymorphone is a semisynthetic opioid created from manipulating morphine, which is derived from poppies. Trial Tr. at 180:7–10. In 1997, Endo sold oxymorphone in intravenous and suppository

formulations. *Id.* at 179:24–25. Both of these formulations provided pain-relief to patients, but were not very profitable. *Id.* at 180:17–18. Thus, Endo was eager to see whether oxymorphone could be developed into a controlled release tablet which patients could take to manage chronic pain at twelve-hour intervals. *Id.* at 406:3–5. Endo believed that if such a product could be developed, it would capture a portion of the then-estimated \$650 million market for opioid painkillers. See Alliance Committee Meeting Overheads (July 10, 1998) (PTX-0217 at 383).

Oxymorphone had been sold in tablet form between 1959 and 1971 as the branded-drug Numorphan. Trial Tr. at 180:3–4; 1458:7–9. It was pulled from the market in 1971 because of poor sales. Regulatory Background (PTX-0115 at 406). Like the intravenous and suppository formulations of oxymorphone, Numorphan had been an immediate-release drug. Trial Tr. at 1458:11–12. An immediate release drug, when swallowed or otherwise administered, releases almost all of its active ingredient within an hour. Trial Tr. at 176–177; *see also* '122 Patent at 3:20–30. In contrast, a controlled-release drug releases the active ingredient over many hours. *Id.* at 178:12–18. In 1997, when Endo began developing its new product, there had never been a controlled-release formulation of oxymorphone. Briefing Package to FDA (Apr. 6, 2000) (PTX-0223 at 428-31).

Developing oxymorphone into an effective controlled-release formulation presented a number of challenges. First among these was a relative lack of previous research into orally administered oxymorphone's pharmacokinetic

effects, meaning the drug's impact on the human body. *Id.* at 177:3-4. At the time of Endo's development work for oxymorphone there were already two controlled-release opioid painkillers on the market, MS Contin and OxyContin. *Id.* at 204:8-20. Those products were controlled-release formulations of morphine and oxycodone, both of which had been studied extensively in human subjects in their immediate release formulations. *See id.* In contrast, only four studies had been conducted on the effects of orally administered oxymorphone in humans, and each of those had been completed before 1983. *Id.* at 201:9-12; *see also* Briefing Packet (PTX-0223 at 410). Thus, unlike with the development of MS Contin and OxyContin, Endo faced an almost total lack of pharmacokinetic data to use in developing controlled-release oxymorphone. Trial Tr. at 201-02.

This lack of pharmacokinetic data made it difficult for Endo's development team to predict in advance whether oxymorphone would be suitable in a controlled-release form. Oxymorphone in immediate-release form has an exceptionally low bioavailability of only about 10%. *Id.* at 194:9-11. This means that when ingested, 90% of the oxymorphone is metabolized by the liver and only 10% actually enters the bloodstream to provide pain relief. *Id.* This is starkly different from morphine and oxycodone, which exhibit bioavailability of 40% and 60-87% respectively. *See id.* at 2611:6; 2613:21-22. Oxymorphone's unusually low bioavailability in immediate release form raised doubts that it would work in a controlled release setting, where far less of the tablet is dissolved at any given time. *Id.* at 190:8-15.

Endo partnered with another company, Penwest Pharmaceuticals, to

develop oxymorphone into a controlled-release tablet. Trial Tr. at 190. Penwest specialized in the development of pharmaceutical formulations. *Id.* It had invented a technology, called TIMERx, which used natural gums to slow the release of a drug's active ingredient over a period of many hours. *Id.* at 303:12–17. With Penwest as partner, by 1998 Endo had developed tablets of controlled-release oxymorphone hydrochloride (which is oxymorphone in its salt-form). See Project Team Minutes (Feb. 12, 1998) (PTX-0157 at 423–24).

Between 1998 and 2001, Endo tested its new formulation in both laboratory settings (*in vitro* testing) and in human subjects and patients (*in vivo* testing). See Project Team Minutes (Feb. 12, 1998) (PTX-0157 at 2) (discussing dissolution testing); see also Alliance Committee Meeting Minutes (May 2, 2001) (PTX-144) (discussing clinical studies). On October 15, 2001, Endo filed applications with the United States Patent and Trademark Office for patents covering its new controlled release oxymorphone product. See United States Patent 3,309,122 at 1 (PTX-0001 at 372); United States Patent 8,329,216 at 1 (PTX-0005 at 463). Shortly thereafter, in December of 2002, Endo filed a New Drug Application (“NDA”) with the Food and Drug Administration for the branded drug OPANA[®]ER. Trial Tr. at 220:2–3.

An NDA is required to obtain regulatory approval to sell branded drugs in the United States. *Id.* at 597:6–11. The new-drug applicant must prove to the FDA, through extensive clinical testing, that the drug is both safe and effective. Cf. 21 U.S.C. § 355(b)(1). Moreover, the applicant must inform the FDA of the patents covering the new drug. See *id.* Upon approving the new drug for sale, the

FDA will list all of the patents covering the product in a publication titled “Approved Drug Products with Therapeutic Equivalence Evaluations,” commonly referred to as the “Orange Book.”

There is an expedited process when seeking FDA approval of a generic version of a branded drug. The generic manufacturer will file an Abbreviated New Drug Application (“ANDA”) with the FDA. This eliminates the need to conduct extensive clinical trials. The generic manufacturer need merely show that the generic drug has the same active ingredient as the branded-drug, and that the two products are bioequivalent. 21 U.S.C. §355 (j). Moreover, the applicant must certify to the FDA that the patents listed in the Orange Book as covering the branded drug do not preclude approval of the generic drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii). One way of doing this is to certify that the patents are invalid, or that the proposed generic product would not infringe those patents. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). This type of certification is known as “Paragraph IV” certification. Once a generic manufacturer files a Paragraph IV certification, it must inform the patent holder of the filing. *Id.* This gives the patent holder a period of time in which to bring a lawsuit asserting the patents. *Id.* If the patent holder brings suit, FDA approval of the generic drug will be stayed for 30 months. 21 U.S.C. § 355(j)(5)(B)(iii).

As discussed, Endo filed its New Drug Application for OPANA®ER in December of 2002. Trial Tr. at 220. That NDA would not be approved until 2006, four years later. *Id.* at 185:20–22. In the meantime, Endo continued to perform development work on the OPANA®ER product. *Id.* at 220. Concerned about the

public's abuse of prescription opioids, Endo began exploring ways to make OPANA®ER tamper resistant. *See id.* at 221:10–13. Project team meetings from this time reveal that Endo had considered a number of mechanisms for deterring abuse of OPANA®ER once it was approved by the FDA for sale, including the use of “antagonists,” agents in the drug formulation that would block the effect of the opioid if the tablet were tampered with. *Id.*; *see also* PowerPoint Presentation “Opioid Abuse Deterrent (OAD) In-Depth Review” (Dec. 7, 2005) (PTX-0922 at 6). Endo also considered making its tablets difficult to crush, so that the drug would be difficult to sniff or inject. Trial Tr. at 221–22. However, these early efforts were unsuccessful. Trial Tr. at 222.

Things began to change in 2006. In that year, the FDA finally approved Endo's NDA for OPANA®ER. Trial Tr. at 794:18–21. Endo launched the product in August of 2006, and it began to be prescribed by physicians across the country. *See id.* However, Endo remained concerned about the growing abuse of prescription opioids. *Id.* at 796:15–20. Recreational drug abusers would crush OPANA®ER and other opioids and sniff the resulting powder to achieve a euphoric effect. *Id.* Therefore, Endo continued to seek partners for developing a crush-resistant version of the drug. *See* Trial Tr. at 797–98.

Endo found such a partner in Grünenthal GmbH. Grünenthal had developed a process for creating tablet pills with an exceptionally high breaking strength, and also integrating other abuse-deterrent features. Trial Tr. at 1053:1–7. Following the launch of OPANA®ER, Endo sent a delegation to Grünenthal's offices in Germany. *Id.* at 1054:20–21. There, Grünenthal

demonstrated that its technology could be used to create tablets that were exceptionally hard. *Id.* at 155. Moreover, Dr. Bartholomäus, one of the inventors of the technology, showed that the tablets were also effective in releasing the active ingredient of the drug for legitimate use. *Id.* at 1055:22–25. Impressed by this presentation, Endo eventually entered into a license agreement with Grünenthal to use its technology to develop a crush-resistant formulation of the recently-introduced OPANA®ER product. *Id.* at 1056:9–11; *see also* Development, License and Supply Agreement between Grünenthal GmbH and Endo Pharmaceuticals Inc. (Dec. 18, 2007) (PTX-0551).

After its launch in 2006, the original formulation of OPANA®ER became one of Endo's core products. Trial Tr. at 788:16–18. Net sales of the drug were \$5 million in 2006, and by 2011 had grown to \$384 million. Trial Tr. at 805:20–25. The high sales of OPANA®ER in 2011 (\$384 million) marked a dramatic increase from the previous year's sales of \$240 million. *See id.* at 806–07. But sales in subsequent years tapered off, amounting to \$198 million in 2014. *Id.* at 806:4.

Endo's crush-resistant formulation of OPANA®ER, which it had been developing with Grünenthal, was approved for sale in the United States at the end of 2011. *Id.* at 807:13. Endo launched the new, crush-resistant formulation of OPANA®ER (OPANA®ER CRF) in early 2012. Trial Tr. at 2021:24. Endo then discontinued the sale of the original, non-crush-resistant formulation of OPANA®ER.

In 2012, the Patent and Trademark Office awarded the three patents at

issue in these cases. The '122 and '216 patents cover Endo's invention of a controlled release oxymorphone tablet. The '060 Patent covers Grünenthal's invention of a hard, crush-resistant tablet which also accommodates secondary barriers to abuse.

Defendants are generic drug manufacturers. Each has filed an Abbreviated New Drug Application with the FDA seeking approval to market generic versions of OPANA®ER in its crushable or non-crushable formulations. *See* Trial Tr. at 697:21; 1134; *see also* Summary Chart (PTX-3562) (listing the ANDA numbers for each defendant). Actavis and Sun Pharma sought FDA approval to market both crushable and crush-resistant generic versions of OPANA®ER. Trial Tr. at 599:18-21. Roxane sought approval solely for the crushable version. *See id.* at 600:4-6. Amneal, Teva, Impax, and ThoRx sought approval solely to manufacture crush-resistant generic products. *Id.* at 598:20-23 (referring to PX-4002.80). To date, the FDA has approved the crushable-product ANDAs filed by Actavis and Roxane, but only Actavis has brought its generic product to market. Trial Tr. at 600:3-7.

Between 2012 and 2013, plaintiffs filed lawsuits against each of the defendants for patent infringement. As many as seven patents have been asserted in this case at various times, involving scores of patent claims. However, as trial approached the parties mutually narrowed the number of patents and patent claims asserted. *See, e.g.,* Stipulation and Order Re U.S. Patent 7,851,482 (Doc. #96 in 12-CV-8060). Moreover, on March 17, 2015, the court dismissed one of the patents from the case on collateral estoppel grounds. *See* Order of

March 17, 2015 at 6. Thus, the bench trial involved only the '122, '216, and '060 patents.

Discussion

In an action for patent infringement, it is the plaintiff's burden to prove by a preponderance of the evidence that every limitation of the asserted patent claims is found in the accused device. *Siemens Med. Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997). "The preponderance of the evidence standard requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence" *Bosies v. Benedict*, 27 F.3d 539, 542 (Fed. Cir. 1994) (internal quotation marks and citations omitted).

A defendant asserting the invalidity of the patents-in-suit carries a higher burden. The defendant must prove the patents' invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011). "Clear and convincing evidence is such evidence that produces 'an abiding conviction that the truth of the factual contentions are highly probable.'" *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

A. Whether Defendants Infringe the Patents-in-Suit.

Determining patent infringement is a two-step process. First, the court must construe the asserted patent claims. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). Second, the claims as construed must be

compared to the accused device. *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993). The accused device will infringe if it “embodies every limitation of the claim, either literally or by an equivalent.” *Id.*

1. Step One: Construing the Asserted Claims.

The first step in the infringement analysis is to construe the asserted patent claims. The purpose of construing the patent claims is not to rewrite the patent, but to simply elaborate on “normally terse claim language” to aid in comprehension thereof. *Terlep v. Brinkmann Corp.*, 418 F.3d 1379, 1382 (Fed. Cir. 2005). The words of a patent claim should generally be given their ordinary and customary meaning as would be understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). The primary source of material in determining the claim’s meaning is the intrinsic evidence, meaning the patent specification, the patent claims themselves, and the prosecution history of the patent. *Id.* at 1318. The patent specification may show that the inventor had ascribed meanings to certain words that those words do not ordinarily convey, and had acted as his own lexicographer. *Id.* at 136. In such a case, the inventor’s definition will govern. *Id.* Likewise, the specification may also disavow the scope of a claim term, and such disavowal will also govern. *Id.* It is only after considering the intrinsic evidence of the claim’s meaning that the court may resort to extrinsic evidence, such as dictionaries and treatises, to aid in comprehension of the claim terms. *Vitronics Corp. v. Conceptoronic, Inc.*, 90 F.3d 1576, 1584 n.6 (Fed. Cir. 1996).

Patent claims generally fall into two broad categories: product claims and

method claims. A product claim describes the invention of a physical product, such as a machine or pharmaceutical tablet. A method claim describes a series of steps, or process, constituting the claimed the invention. In construing patent claims, courts “must generally take care to avoid reading [method] limitations into [product] claims . . . because the process by which a product is made is irrelevant to the question of whether that product infringes a pure [product] claim.” *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1344 (Fed. Cir. 2008). That being said, some patent claims describe a product by the process used to achieve it. *See Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1291 (Fed. Cir. 2009). Such “product-by-process” claims should be read to require use of the claimed process. *Id.* at 1294.

Claims may be either independent or dependent. 35 U.S.C. § 112(c). An independent claim stands alone. *Id.* In contrast, a dependent claim refers back to a previous independent claim. *Id.* To establish whether a claim is dependent upon another, the court examines if the new claim both refers to an earlier claim and further limits that referent. *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1357 (Fed. Cir. 2007). Significantly, a dependent claim must be construed to incorporate all of the limitations of the independent claim to which it refers. 35 U.S.C. § 112(d).

Pharmaceutical patent claims generally take one of several common forms. *See* Shashank Upadhye, Generic Pharmaceutical Patent and FDA Law §§ 1:9–1:19. Inventors may choose to claim the active pharmaceutical ingredient (“API”) itself, meaning the actual molecule at the root of the invention. *Id.* § 1:9.

However, because many APIs cannot be used in their pure form, the inventor will claim the API in its salt-form. *Id.* § 1:10; *see also* Trial Tr. at 1457:6–7. Another type of pharmaceutical patent claim is the “release profile claim.” *Id.* § 1:19. A release profile claim recites the amount of an API delivered from a drug at certain intervals. *Id.*

The first step in construing the claims asserted in this case is to define a person of ordinary skill in the art at the time of the inventions. At trial, plaintiffs and defendants provided similar definitions for a person of ordinary skill in the art. Defendants’ expert, Dr. Umesh Banakar, testified that such a person would have “at least a master’s degree or a doctorate in pharmaceutical sciences with experience in developing formulations, including controlled release formulations. If the individual had a lesser degree of training, such as a bachelor’s degree, then he would need several more years of experience in the areas of pharmaceutical formulation development.” Trial Tr. at 1502:13–20. Plaintiffs adopted this definition at multiple points during the proceedings, *see, e.g.*, Trial Tr. at 1692:1–3; 1937:2–6, and the court finds that it is a reasonable one. Thus, a person of ordinary skill in the art would possess the above-described qualifications and experience at the time of the inventions.

a. Construing the Asserted Claims of the ’122 Patent.

The invention embodied in the ’122 Patent is a controlled-release tablet of oxymorphone, effective in providing pain relief over a twelve-hour period. Endo asserts claims 2, 3, 19, and 20 of the ’122 Patent against defendants. Claim 1, upon which Claim 2 depends, reads as follows:

1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and a controlled release delivery system comprising at least one pharmaceutical excipient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

'122 Patent at 25:50–60.

The intrinsic evidence provides clarity as to how Claim 1 would read to a person of ordinary skill in the art at the time of the invention. First, the claim calls for an “analgesically effective controlled release pharmaceutical composition in the form of a tablet.” ’122 Patent Claim 1. A “tablet” is a solid oral dosage form. *Id.* at 3:5. Analgesia is a dulling of the sensation of pain. *See* ’122 Patent at 1:15–24. While the patent calls for analgesia, it does not encompass any pain relief regardless of how slight. *See id.* at 4:41–45. Rather, the patent calls for the *effective* dulling of pain. *See id.* at 25:50. The substance must provide pain relief at a level sufficient to treat patients suffering from chronic illnesses. *Id.* at 1:39–40. This means it must treat moderate, severe, or acute chronic pain. *Id.* at 44:43–46. Indeed, the specification defines how much oxymorphone is needed to enter the bloodstream for the dosage form to be considered “effective.” *See id.* at 3:41–53. Thus, a person of ordinary skill in the art would read the terms “analgesically effective controlled release pharmaceutical composition in the form of a tablet” as: a tablet providing pain relief at therapeutically useful levels. *See id.* at 3:4–6.

A “controlled release pharmaceutical composition” is a drug formulation that releases its active ingredient slowly. The specification explains the concept of controlled release drugs by comparison to immediate release drugs. *Id.* at 3:19–33. An immediate release tablet, when dissolved in an environment akin to the human digestive system, releases more than 80% of its active ingredient within 30 minutes. *Id.* at 26. In contrast, a controlled release tablet generally lasts much longer, releasing no more than 80% of its active ingredient in 60 minutes. *See id.* at 3:30–34. Thus, a “controlled release pharmaceutical composition” is a drug formulation that releases its active ingredient slowly over time.

A “dosing interval” refers to length of time between doses of a drug. The specification explains that when a drug is taken by a patient, its effects wear off over time, requiring the patient to take another dose. *Id.* at 1:40–43. The length of time between doses, then, is the dosing interval. *See id.* Claim 1 of the ’122 Patent calls for a “twelve hour dosing interval.” *Id.* at 25:51. This means that the when a patient takes a dose, it will last for twelve hours before another dose is needed.

Claim 1 requires the tablet to be comprised of “oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet.” *Id.* at 25:53–54. Oxymorphone is an opioid analgesic. *Id.* at 1:25. Like many opioids, oxymorphone may be paired with a non-toxic salt for use in medicine. *Id.* at 4:56–62. A “pharmaceutically acceptable salt” of oxymorphone would be oxymorphone hydrochloride, or other salts formed by mixing oxymorphone with acids such as sulfuric acid, nitric acid, and others. *Id.* at

4:58–68. Thus, the patent requires a tablet containing oxymorphone or a salt of oxymorphone as the sole active ingredient.

Claim 1 also requires that the tablet comprise a “controlled release delivery system comprising at least one pharmaceutical excipient.” *Id.* at 25:53–56. As discussed, “controlled release” means that a drug’s active ingredient releases slowly over time. “Delivery system” refers to the vehicle used to provide the controlled release property. *See id.* at 5:48–62. Such systems include “osmotic pumps”; use of a coating of controlled release film; or use of a “controlled release matrix.” *Id.* at 5–6. An “excipient” is a substance other than the active ingredient. *See id.* at 6:1–2. In the context of this claim, it is the excipient (not the oxymorphone) which provides the controlled-release delivery properties of the tablet. *Id.* at 25:54–55.

Claim 1 further provides that “upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C, about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.” *Id.* at 55–60. “In vitro dissolution test” refers to laboratory testing, as opposed to human testing (*in vivo*), of the rate at which a substance dissolves. *See id.* at 3:34–42. “RPM” means revolutions per minute, and pH is a measure of acidity. *Id.* at 464:10–11; 469:1–2. The term “USP Paddle Method” is not defined in the specification. However, a person of ordinary skill in the art would know that “USP” stands for United States Pharmacopeia, a book describing standard formulation methods. Trial Tr. at 467:16–18.

The United States Pharmacopeia describes two dissolution testing methods relevant to this litigation, each of which uses a different dissolution testing apparatus. See The National Formulary, The United States Pharmacopeia (1995 ed.) (PTX-0909 at 1792). The first apparatus consists of vessel filled with a fluid. *Id.* at 1791. A metal rod with a basket attached is lowered into the vessel and spun. *Id.* Inside the basket is a tablet. *Id.* As the basket spins in the fluid, the tablet will dissolve. *Id.* This method of dissolution testing, using a basket-apparatus, is known as the “basket method.” See Figure 1 Below. *Id.* at 1792.

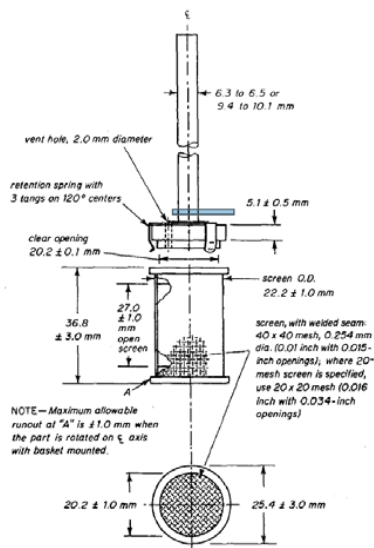


Fig. 1. Basket Stirring Element.

The second apparatus is similar to the first apparatus. However, the second apparatus uses a “paddle,” which is formed from a blade, as the stirring element. *Id.* In this method, the tablet is not contained within a basket, but rests at the bottom of the vessel. *Id.* As the paddle spins above the tablet, the tablet will dissolve. See *id.* This method of dissolution testing, using a paddle, is known

as the “paddle method.” See Figure 2 Below. *Id.*

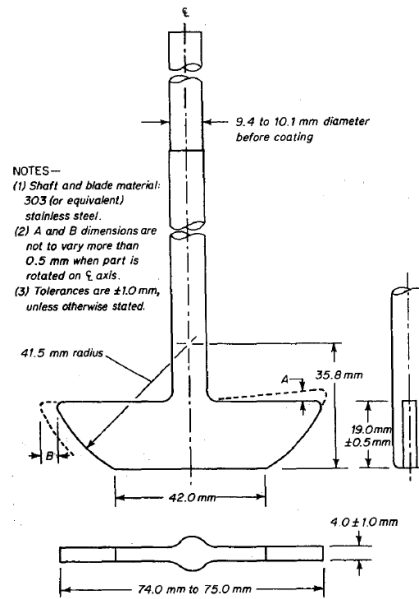


Fig. 2. Paddle Stirring Element.

Thus, a person of ordinary skill in the art would understand the term “USP Paddle Method” as referring to a specific dissolution test described in the United States Pharmacopeia, one that uses a vessel filled with a fluid which is stirred by a blade-shaped paddle.

Finally, the remainder of Claim 1 describes the rate at which the tablet releases the active ingredient using the method described. This language is clear: “about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.”

The release rate is further elaborated in claims 2 and 3 of the '122 Patent. Claim 2 provides that at four hours into the test, “about 45% to about 80%” of the oxymorphone is released. '122 Patent at 25:60–64. Claim 3 provides that at

10 hours into the test, “about 80%” of the oxymorphone is released. *Id.* at 25:65–67.

In sum, Claim 1 of the ’122 Patent would, to a person of ordinary skill in the art at the time of the invention, read as follows: “a controlled-release pharmaceutical tablet providing pain relief at therapeutically useful levels for twelve hours, consisting of oxymorphone (or its salt) as the sole active ingredient, and also consisting of a controlled-release delivery system made up of a non-oxymorphone substance that, when tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, releases about 15%–50% of the oxymorphone (or its salt) by about an hour into the test.” Claim 2 would be read as providing that about 45%–80% of the oxymorphone will be released by about four hours into the test. Finally, Claim 3 provides that about 80% of the oxymorphone will be released by about ten hours into the test.

Endo also asserts Claim 20 of the ’122 Patent against defendants. Claim 20 depends from Claim 18. Taken together, the two claims read:

18. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 1 comprising about 5 mg to about 80 mg of oxymorphone or pharmaceutically acceptable salt thereof.

20. The method of claim 18 wherein upon oral administration of the composition the oxymorphone AUC_(0-inf) is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.

’122 Patent at 26:54–58.

The construction of the term “administering” was hotly debated at trial.

Defendants argued that as mere drug manufacturers, they do not actually administer tablet pills to subjects or patients, and thus cannot infringe the method claims of the '122 and '216 patents. *See, e.g.*, Trial Tr. at 611–13. While this argument presents issues of claim construction, it also implicates questions of infringement and indirect infringement, which will be dealt with in subsequent sections of this decision. *See infra* Part A(2)(a)(ii). As matter of claim construction, the meaning of the term “administering” would be readily apparent to a person of ordinary skill in the art upon reading the specification.

The specification uses the term “administering” in two contexts. In the first context, “administering” is used synonymously with the unsupervised “taking” of the drug by patients in order to enjoy long periods of pain relief. *See, e.g.*, '122 Patent at 1:39–41; 4:41–48. In the second context, the term “administering” implies a clinical or laboratory setting, wherein an actor, such as a physician or scientist, gives, or more specifically *feeds*, tablet pills to a patient and then observes the results. *See, e.g., id.* at 20:53–55 (beginning on the morning of Day 3, the volunteers were administered a . . . tablet every 12 hours . . .). Both of these contexts are relevant to claims 18 and 20 of the '122 Patent. Claim 18 recites “a method of treating pain in a subject in need thereof, the method comprising *administering* to the subject the pharmaceutical composition of claim 1.” *Id.* at 26:54–56. A person of ordinary skill in the art would understand the “administering” requirement to mean when the subject *takes* the tablet to treat his or her pain, and also when another actor *feeds* the tablet to the subject to treat his or her pain.

Claim 20 incorporates the method of “administering” the tablets described in claim 18, and then provides that “upon oral administration of the composition the oxymorphone $AUC_{(0-inf)}$ is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.” *Id.* at 28:1–5. Consistent with the claim construction above, “oral administration” means a subject’s *taking* of the tablet by mouth, or the *feeding* of a tablet to a subject to be taken by mouth.

The term “AUC” means “area under the curve,” and is a way to measure the concentration of a drug in the bloodstream for a stated period of time, as signified by the subscript within the parenthesis. *See id.* at 11:36–40. Thus, $AUC_{(0-inf)}$ means “area under the curve,” or concentration of drug in the blood, from zero hours to infinity. *Id.* at 11:40–43. The terms “fed” and “fasted” refer to whether a person has eaten or not. *See id.* at 13:67–14:1 (describing that for a particular study, “fed” patients were those who had eaten a high-fat breakfast). Putting the above constructions together, Claim 20 of the ’122 Patent reads as follows: “A method of treating pain in which the subject, upon taking or being fed the tablet orally, exhibits total blood concentration levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the tablet on an empty stomach.”

The final asserted claim of the ’122 Patent is Claim 19. Claim 19 reads as follows:

19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or pharmaceutically acceptable salt

thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

'122 Patent at 26:59–27:7. Most of Claim 19 simply restates limitations already recited in claims 1, 2, and 3 of the '122 Patent. Claim 19 differs, however, in that it provides that the controlled release delivering system comprises “a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid.” *Id.* at 26:63–65. “Hydrophilic” is not defined in the specification, but a person of ordinary skill in the art would understand it to mean “water-loving,” or something that absorbs water. Trial Tr. at 1475:13-15. Upon exposure to gastrointestinal fluid, the water-absorbing material forms a gel which releases oxymorphone slowly. See '122 Patent at 6:48–55. In sum, Claim 19 would read the same way as claims 1, 2, and 3 of the '122 Patent, but recites the additional limitation that the controlled release delivery system be comprised of a hydrophilic substance which forms a gel upon exposure to gastrointestinal fluid.

b. Construing the Asserted Claims of the '216 Patent.

The '216 Patent is similar to the '122 Patent, and in fact contains the exact same specification. Consequently, where the two patents share certain language, a person of ordinary skill in the art would interpret that language the same way for both patents. Moreover, many of the asserted claims of the '216 Patent are

repetitive, and repeat the same limitations in different combinations. For these reasons, the court will construe terminology appearing in the '216 Patent claims in the first instance, but where terminology has already been construed, will generally apply the earlier construction. In all, Endo asserts sixteen claims from the '216 Patent, claims 1, 22, 40, 42, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82. Those claims, as well as seven independent claims incorporated therein by reference (claims 21, 38, 49, 55, 66, 72, and 77), are construed below.

Claim 1 of the '216 Patent reads as follows:

1. An oral controlled release oxymorphone formulation, comprising:
 - a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
 - b. a hydrophilic material,wherein upon oral administration of the formulation to a subject in need of an analgesic effect:
 - (i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
 - (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
 - (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 \text{ to } \infty)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;
 - (iv) the duration of the analgesic effect is through at least about 12 hours after administration; and
 - (v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

'216 Patent at 26:35–55. A person of ordinary skill in the art would understand parts (a) and (b) of the claim as describing a formulation of oxymorphone or its salt combined with a hydrophilic substance. When that formulation is taken by or fed to a subject in need of pain relief, it will produce the effects described in subparts (i) thorough (v).

Subpart (i) states that the formulation “provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone.” ’216 Patent at 26:42–43. “Blood plasma level” refers to the amount of a substance in the bloodstream. *Cf. id.* at 2:8–14. 6-OH oxymorphone has a technical definition as “the analog of oxymorphone having an alcohol (hydroxy) moiety that replaces the carb oxy moiety found on oxymorphone at the 6-position.” *Id.* at 2:65–3:2. While this is the definition a person of ordinary skill in the art would apply, it may be helpful to the reader to explain what 6-OH oxymorphone is in plain terms. At trial, a number of experts explained that 6-OH (or “six-hydroxy”) oxymorphone is a byproduct produced when oxymorphone is metabolized in the human liver. *See, e.g.,* Trial Tr. at 592:2–6. This byproduct, known as a “metabolite,” will have a measurable presence in the bloodstream. *See id.* at 592–93. Thus, subpart (i) of Claim 1 of the ’216 Patent simply means that the formulation will provide detectable levels of the metabolite 6-hydroxy-oxymorphone and oxymorphone in the bloodstream.

Subparts (ii) through (v) of the claim define what those levels will be. Subpart (ii) explains that the blood levels of 6-hydroxy-oxymorphone and oxymorphone will “peak” within about 1 to about 8 hours after administration. ’216 Patent at 26:44–46. At trial, there was some dispute among the experts as to what the term “peak” meant. *See* Trial Tr. at 1575:7–10. But such debate is academic in light of the specification. The specification refers to “peaks” of curves as drawn on charts. *See* ’216 Patent at 12:58–67. Upon looking at the charts, one of ordinary skill in the art would immediately recognize a “peak” as occurring

where blood concentration reaches a high-point before declining. See Figure 5 below.

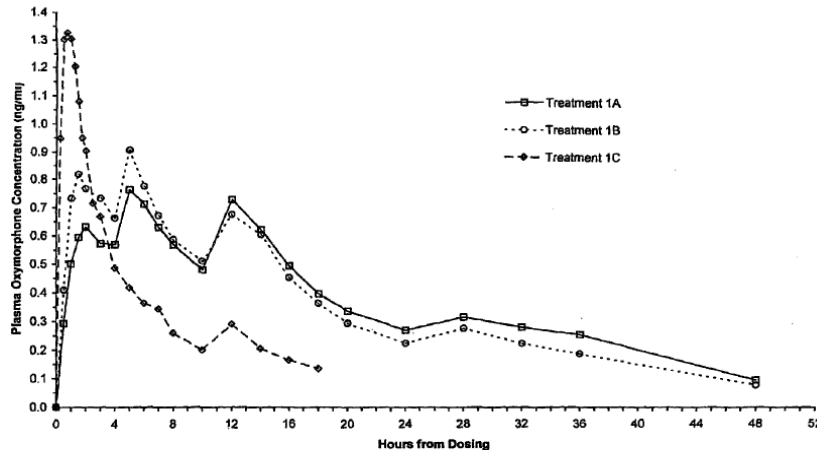


Figure 5

'216 Patent at "Sheet 5."

Subpart (iii) provides that "the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 \text{ to } \infty)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5." '216 Patent at 26:47-51. This means that upon measuring the total amount of 6-hydroxy-oxymorphone (the metabolite) in the bloodstream over time, and comparing that amount to the total amount of oxymorphone in the bloodstream over time, there will be between half to 50% more 6-hydroxy-oxymorphone in the bloodstream than oxymorphone in the bloodstream. *Cf. id.* at 3:51-53.

The final subparts of Claim 1 are clear. Subpart (iv) provides that the pain killing effect of the formulation will last about twelve hours; and subpart (v) provides that the blood plasma level of oxymorphone will exhibit two or three

peaks, or high-points, within twelve hours of administration. *See id.* at 26:52–54.

Claim 21 of the '216 Patent is similar to claims asserted in the '122 Patent.

Claim 21 provides:

21. A pharmaceutical tablet prepared by:
- a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and
 - b. forming the tablet,
- wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours.

'216 Patent at 28:10–22.

A person of ordinary skill in the art would understand part (a) of Claim 21 as describing a tablet made by mixing oxymorphone or its salt with a substance to slow release of the active ingredient. Part (b) calls for “forming” the tablet. “Forming” is not explicitly defined in the specification, but is used in contexts implying a meaning synonymous with “making.” Indeed, the specification states that the invention “includes a method of making an oxymorphone controlled release . . . form . . . which comprises mixing the particles of oxymorphone . . . with granules comprising the controlled release delivery system.” *Id.* at 4:52-57. It then says that a preferred means of doing this is to “directly compress the mixture to form tablets.” *Id.* This latter step, compression, is embodied in Claim 13. *See id.* at 27:38–39. But as used in Claim 21, the phrase “forming the tablet” simply means “making the tablet.”

The remainder of Claim 21 would be understood as requiring that when

tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, the tablet releases about 15%–50% of the oxymorphone (or its salt) by about an hour into the test, and that when taken by or fed to a human subject, the tablet will provide pain relief for 12 to 24 hours. *See id.* at 28:15–23.

Claim 22 depends from Claim 21, and further describes the rate at which the dosage form will release the active ingredient over time. *Id.* at 28:23–27. The tablet will release about 45% to about 85% of the oxymorphone or its salt at about 4 hours in the test, and will release about 80% of the oxymorphone at about 10 hours into the test. *Id.*

Claim 38 is a method claim, and reads as follows:

38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

- (a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test; and
- (b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.

'216 Patent at 29:49–30:5.

Parts (a) and (b) of Claim 38 require the “providing” and “administering” of the dosage form to a person in need of acute or chronic pain relief. *Id.* Because the terms “providing” and “administering” are used separately in Claim 38, those terms, as a matter of construction, have distinct meanings. It has already been established that “administering” involves either the *taking* of a dosage form by the subject, *see, e.g.*, ’216 Patent at 4:42–43 (discussing the taking of two or three doses daily to manage pain), or the *feeding* of a dosage form to the subject by another actor. *Id.* at 5:13–14. Such an actor might be a scientist who *feeds* tablets to subjects in conducting a study. *See, e.g.*, ’216 Patent at 5:9–18.

Because “administration” involves the taking or feeding of the dosage form, it represents a terminal point in the process described in Claim 38. Since this is the termination of the process, then “making” the dosage form marks some distant beginning (although it is not a part of the actual method claim). The specification speaks of “making” the dosage form in terms of actually manufacturing it, or actually mixing oxymorphone or its salt with a controlled release delivery system. *See, e.g.*, ’216 Patent at 4:51–58; 28:10–14.

“Providing” the dosage form, then, must come before administering in the method recited in Claim 38. The dosage form must first be made (manufactured), then provided to the subject, and then administered to subject. *Id.* at 29:50–30:1–2. In this context, “providing” is synonymous with “making available.” After the dosage form is manufactured, it is made available (provided) to a subject who takes it or has it fed to him by another person. Thus, the court construes the

term “providing” as the “making available” of the dosage form described in the claims.

The remainder of Claim 38 covers familiar ground. The claim requires, in subpart (a), the making available to subjects of a 5mg to 80mg controlled-release dosage form of oxymorphone or its salt, with a release rate “designed to provide”¹ sufficient blood levels to achieve pain relief over a 12 hour period, and that when tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, the oxymorphone will be released about 15%–50% at about one hour in the test, about 45%–80% at about fours in the test; and at least 80% at about 10 hours into the test. ’216 Patent at 29:50–67. Subpart (b) of Claim 38 requires the taking or feeding of a single dose by or to a subject. *Id.* at 30:1–2.

Finally, Claim 38 requires that once the dose is provided and administered, “the oxymorphone C_{\max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.” “ C_{\max} ” means the maximum observed concentration of a drug in the bloodstream. ’216 Patent at 11:44. It measures concentration of the drug at its highest single point, and consequently is different than the measurement of “AUC,” or area under the curve, which measures the concentration of the drug in the blood over a stated period of time. *See id.* at 11:40–43. Thus, this portion of the claim would be understood by a person of ordinary skill in the art as meaning “the maximum

¹ The parties agree that “designed to provide” means simply “that provides,” and does not require a specific intention. *See* Second Stipulation and Order (Apr. 9, 2015) ¶¶ 1–2.

observed concentration of oxymorphone in the bloodstream is at least 50% percent higher when the dosage form is taken by (or fed to) a subject after having eaten a meal than it would be on an empty stomach.”

Claim 40 of the '216 Patent depends from Claim 38, and recites the additional limitation that “the difference in the oxymorphone area under the curve $AUC_{(0-inf)}$ between fed and fasted conditions is less than 20%.” *Id.* at 30:10–12. As discussed above, this language would be understood by a person of ordinary skill in the art as meaning that, having taken the dosage form, the subject will exhibit total blood concentration levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the dosage form on an empty stomach.

Claim 42 also depends from claim 38, and reads as follows:

42. The method of claim 38 wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

- (i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
- (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and
- (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0-inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

Id. at 30:15–27. A person of ordinary skill in the art would understand part (i) of the claim to require that the dosage form provide detectable levels of 6-hydroxy-oxymorphone (the metabolite) and oxymorphone; and would understand part (ii) to require that the levels of both 6-hydroxy-oxymorphone and oxymorphone “peak,” or reach a high-point, within 1 to 8 hours after the dosage form is taken.

Finally, a person of ordinary skill in the art would understand part (iii) to require that the ratio of 6-hydroxy-oxymorphone to oxymorphone in the bloodstream will be between about 0.5 to 1.5.

Claims 49, 50, and 54 of the '216 Patent are composition claims with terms already construed in the preceding paragraphs of this decision. The claims read as follows:

49. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

- a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and
- b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

50. The composition of claim 49 wherein upon oral administration thereof the oxymorphone $AUC_{(0-inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

54. The composition of claim 49 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

'216 Patent at 30:52–31:26.

Claim 49 would be understood by a person of ordinary skill in the art as

describing a pharmaceutical composition of 5mg to 80mg of oxymorphone or its salt to be taken orally and which provides, in a controlled or “slow” fashion, pain relief at therapeutically useful levels over a twelve hour period. The maximum concentration of oxymorphone in the blood will be at least 50% higher when the dose is taken after eating a meal as opposed to on an empty stomach. The composition would, when tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, release about 15% to about 50% of the oxymorphone or its salt at about an hour into the test.

Claim 50 would be understood as stating the additional limitation that the composition of Claim 49, upon being administered, will produce total blood concentration levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the tablet on an empty stomach. Finally, Claim 54 would be understood to mean that the composition of Claim 49, upon being tested using the Paddle Method at 50 revolutions per minute and under certain other conditions, would release about 45% to about 80% of the oxymorphone at about 4 hours in the test, and would release about 80% of the oxymorphone or its salt at about 10 hours in the test.

Claim 55, 57, 62, 64, and 66 of the '216 Patent are also composition claims whose terms were construed in the previous sections of this decision. Together, those claims read as follows:

55. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:
 - a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone over at least 12 hours to provide sustained pain relief over this same period;

- and
- b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

57. The composition of claim 55; wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

62. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

64. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

66. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

- a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and
- b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, and wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.

'216 Patent at 31:27–32:50.

Parts (a) and (b) of Claim 55 are nearly identical to Claim 49, except that part (a) contains the additional language: “a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of *oxymorphone and 6-hydroxy-oxymorphone* over at least 12 hours to provide sustained pain relief over this same period.” *Id.* at 31:29–34 (additional language in italics). A person of ordinary skill in the art would understand this language to mean a delivery system that releases the active ingredient slowly over time that provides adequate blood plasma levels of oxymorphone or 6-hydroxy-oxymorphone (the metabolite) over at least 12 hours to provide sustained pain relief over this same period.

The remainder of Claim 55 would be understood to mean that upon testing the composition in the laboratory using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, the composition will release about 15% to about 50 of the oxymorphone or its salt at about one hour in the test.

Claim 57 depends from Claim 55, but recites narrower dissolution ranges when the composition is tested using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature. *See* '216 Patent

at 49–67. The claim provides that the oxymorphone or its salt will be released at the following rates: at least 27% at about 1 hour into the test; at least 40% at about 2 hours into the test; at least 50% at about 3 hours into the test; at least 64% at about 5 hours in the test, at least 70% at about 6 hours in the test, at least 79% at about 8 hours in the test, at least 85% at about 10 hours in the test, and at least 89% at about 12 hours in the test. *Id.* at 31:52–67.

Claims 62 and 64 would be understood as simply restating, in individual fashion, two of the dissolution limitations already recited in Claim 57. *Compare id.* at 32:18–21 and 32:26–29 *with* 31:59–65. Specifically, Claim 62 requires that the composition of Claim 55 release at least 70% of the oxymorphone or its salt at about 6 hours into the test; and Claim 64 requires that the composition of Claim 55 release at least at least 85% of the oxymorphone or its salt at about 10 hours in the test.

Claim 66 is almost identical to Claim 55, except that part (a) of Claim 66 omits the language “of oxymorphone and 6-hydroxy-oxymorphone” contained in part (a) of Claim 55. *See* ’216 Patent at 32:37–38. Additionally, Claim 66 provides that: “wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.” *Id.* at 32:48–50. As discussed above, a “peak” would be recognized by a person of ordinary skill in the art as occurring when blood concentration of oxymorphone reaches a high-point before declining. The last clause of Claim 66 would be understood, then, as requiring that blood plasma levels of oxymorphone reach one or more high-points after the composition is taken by or fed to a human

subject.

Claim 71 depends from Claim 66, and provides that the composition be in tablet form, and release about 45% to about 80% of its oxymorphone or its salt at about 4 hours in the test, and at least about 80% of the oxymorphone or its salt at about 10 hours in the test. See '216 Patent at 33:8–14.

Claim 72 of the '216 Patent describes a composition of oxymorphone that uses a “controlled release matrix . . . of a gelling agent which forms a gel upon exposure to gastrointestinal fluid.” '216 Patent at 33:14–20. Claim 72 reads as follow:

72. A controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test.

Id. at 33:14–26.

The specification explains that a “controlled release matrix” exists when oxymorphone is paired with a certain type of controlled release delivery system. *Id.* 6:48–51. That delivery system consists of a gelling agent. *Id.* at 6:52. The gelling agent is a hydrophilic material, such as xanthan gum, that gels when exposed to gastrointestinal fluid. See *id.* 6:7:12–15. Because the substance forms a gel upon exposure to gastrointestinal fluid, it releases the active ingredient, or oxymorphone, at a controlled rate rather than all at once. See *id.* at 6:50–53.

Thus, a person of ordinary skill in the art would understand the terms “controlled release matrix . . . comprising . . . a gelling agent” to mean the pairing of oxymorphone or its salt with a controlled release delivery system consisting of a gelling agent, a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid which releases the oxymorphone slowly.

The remainder of Claim 72 as provides that between about 10% to about 75% of the controlled release matrix will consist of the gelling agent. '216 Patent at 33:18–19. Moreover, upon being tested in the laboratory using the Paddle Method at 50 revolutions per minute in media of a certain acidity and temperature, about 15% to about 50% of the oxymorphone or its salt will be released at about 1 hour into the test. *Id.* at 33:20–26.

Claims 73 and 74 of the '216 Patent depend from Claim 72, and provide that the composition of Claim 72 will release about 45% to about 80% of the oxymorphone or its salt at about four hours in the dissolution test; and at least 80% of the oxymorphone or its salt after about 10 hours in the test. *See* '216 Patent at 33:27–37.

Claim 77 is an independent claim that brings together many of the limitations discussed earlier. Claim 77 reads as follows:

77. A controlled release pharmaceutical composition comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient, and a controlled release matrix comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50rpm in 500ml media having a pH of 1.2 to 6.8 at 37°C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is

released from the composition after about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test, and at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test, wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{\max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0-\infty)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

'216 Patent at 33:56–34:18.

Claim 77 would be understood by a person of ordinary skill in the art as reciting a pharmaceutical composition with oxymorphone or its salt as the active ingredient paired with a controlled-release matrix, which is a controlled-release delivery system consisting of about 10% to 75% of a gelling agent, a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid. See '216 Patent at 33:56–67. Moreover, Claim 77 would be understood as requiring that the composition, upon being tested in the laboratory using the Paddle Method at 50 revolutions per minute in 500 ml of media of a certain acidity and temperature, will release about 15% to about 50% of the oxymorphone or its salt after about 1 hour in the test, about 45% to about 80% of the oxymorphone or its salt after about 4 hours in the test, and at least 80% of the oxymorphone or its salt after about 10 hours in the test. *Id.* at 34:1–11. Finally, Claim 77 would also be read as providing that upon the composition being taken by or fed to a human subject, the maximum observed concentration (C_{\max}) of oxymorphone in the bloodstream will be at least 50% percent higher after having eaten a meal than it would be on

an empty stomach, and the total blood concentration levels of oxymorphone, as measured by area under the curve, will be no more than 20% higher after having eaten a meal as compared to having taken the tablet on an empty stomach. *Id.* at 34:11–18.

Claim 78 depends from Claim 77, and thus incorporates all of Claim 77's limitations. However, Claim 78 recites a number of additional limitations already construed for Claim 1. See '216 Patent at 26:40–55. To a person of ordinary skill in the art, Claim 78 would be read to mean: the composition of Claim 77 which, when taken by or fed to a subject in need of pain relief, will produce two or three peaks, or high-points, in blood oxymorphone levels within about the first twelve hours. Moreover, part (i) means that the formulation will provide detectable levels of the metabolite 6-hydroxy-oxymorphone and oxymorphone in the bloodstream. Part (ii) explains that the blood levels of 6-hydroxy-oxymorphone and oxymorphone will “peak,” or reach a high-point, within about 1 to about 8 hours after administration. Part (iii) means that after the composition is taken, the total amount of 6-hydroxy-oxymorphone (the metabolite) in the bloodstream over time will be between half to 50% more than the total oxymorphone in the bloodstream. Finally, part (iv) provides that the pain relief will last at least twelve hours.

Claims 79 and 80 recite additional dissolution ranges for the composition of Claim 77. '216 Patent at 34:19–43. A person of ordinary skill in the art would understand the claims as providing that the composition of Claim 77 will release about 58% to about 66% of the oxymorphone or its salt after about 4 hours in the test; and will release about 85% to about 96% of the oxymorphone or its salt

after about 10 hours in the test. *id.*

Claim 82 of the '216 Patent is a method claim reading as follows:

82. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 77 in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof.

'216 Patent at 34:56–60. A person of ordinary skill in the art would understand the claim as follows: a method of treating pain in a subject in need pain relief, by which the subject is fed or takes the composition described in Claim 77 in sufficient amounts as to provide 5mg to about 80mg of the oxymorphone or its salt to the subject.

c. Construing the Asserted Claims of the '060 Patent.

The '060 Patent is the product of co-plaintiff Grünenthal's efforts to invent a dosage form so hard that it is difficult to abuse by crushing, and which also accommodates secondary barriers to abuse. See '060 Patent at 2:26–62. Plaintiffs assert twelve claims of the '060 Patent, claims 1, 4, 9, 24, 25, 27, 29, 30, 31, 32, 33, and 34². Those claims, as well as three independent claims incorporated therein (claims 22, 23, and 28), will be construed in the following paragraphs of this decision.

Claim 1 of the '060 Patent reads as follows:

1. An abuse-proofed, thermoformed dosage form comprising one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C), wherein the polymer (C) has a molecular weight of at least 0.5 million according to rheological measurements, and optionally at least one wax (D), wherein the

² Claim 34 is not asserted against Teva.

dosage form exhibits a breaking strength of at least 500 N.
'060 Patent at 21:6–14.

At trial, the parties identified four areas of dispute regarding the construction of Claim 1 of the '060 Patent: (i) whether the term “abuse-proofed” requires a demonstrated elimination of abuse, or merely a reduction in the potential for abuse; (ii) whether the term “thermoformed” involves the subsequent application of heat; (iii) whether “breaking” involves requires separation of the dosage form into two or more pieces; and (iv) whether Claim 9 requires a separate viscosity increasing agent that forms a gel.

i. The Term “Abuse-Proofed” Means a Reduction in the Potential for Abuse.

Claim 1 recites “an abuse-proofed thermoformed dosage form.” *Id.* at 21:6–7. At trial, the parties suggested different readings of the term “abuse-proofed.” Defendant Actavis argued that the term “abuse-proofed” means that the dosage form must achieve a demonstrated and significant elimination of abuse, and plaintiffs argued that “abuse-proofed” requires merely a reduction in the potential for abuse. *See, e.g.*, Trial Tr. at 1137:7–11; 2151–52.

Plaintiffs’ construction of “abuse-proofed” is correct. The '060 Patent certainly aims to combat abuse of opioids, but the specification makes clear that it does not require a demonstrated elimination of abuse. The specification explains that opioids, because of their efficacy in treating pain, “also have abuse potential,” meaning they can be “used by abusers to induce a state of . . . euphoria,” or a high. '060 Patent at 1:25–32. Abuse is possible when users grind opioid dosage forms in a mortar and sniff the resulting powder, or mix the powder

with water to inject intravenously. *Id.* at 32–49. The purpose of the Grünenthal’s invention was to “*complicate* or prevent the pulverization” of dosage forms to prevent abuse “simply by pulverization.” *Id.* at 2:5–14. To this end, the Grünenthal patent recites a dosage form of exceptional hardness, so hard that “pulverization . . . is considerably more difficult using conventional means” like a hammer, mortar and pestle, or mallet. *Id.* at 2:227–42. Moreover, the Grünenthal invention accommodates the inclusion of additional barriers to abuse, such as irritants to deter snorting, or the use of a “viscosity-increasing agent” to complicate injection. *Id.* at 6:35–54.

This language does not require a demonstrated reduction of abuse, or even the elimination of the ability to crush the dosage form. Rather, it signifies to a person of ordinary skill in the art that the invention intends to *reduce the potential for abuse*, to make it potentially more difficult. *See id.* at 6:24–34. (“In the event of . . . pulverization . . . achieved by application of extreme force, the dosage forms . . . may . . . contain further agents which *complicate* or prevent abuse.” *Id.* at 6:24–34.” But this does not require the showing of a demonstrated actual reduction in abuse.

A person of ordinary skill in the art, upon reading the specification, would understand the term “abuse-proofed” as requiring “a reduction in the potential for abuse.”

ii. The Term “Thermoformed” Allows for the Subsequent Application of Heat.

At trial, the parties vigorously debated the meaning of the term

“thermoformed.” *See, e.g.*, Trial Tr. at 1138:5–9. There is general agreement that “thermoforming” is the creation of a dosage form by applying heat and pressure to mixtures of certain substances. *Id.* at 1250:21; 1339:22–25. First, the formulator mixes the active ingredient with a synthetic or natural polymer of high molecular weight, preferably a “thermoplastic” (heat-softening) polymer such as polyethylene oxide. ’060 Patent at 11:13–14; 5:65–6:2. He may also include in the mixture “an auxiliary substance” intended to deter abuse in ways other than increasing hardness. *See id.* at 6:40–54; 11:15–19. Second, the mixture is formed by applying pressure to it, and by exposing it to heat at some point. This is where the parties disagree. Plaintiffs argue that the heat may be applied before, simultaneously to, or subsequently to the forming the tablet. Defendants argue that thermoforming does not encompass the subsequent application of heat.

The specification indicates that subsequent heat can be used to thermoform. *See id.* at 11:25–39 (“The resultant mixture is preferably formed directly by application of pressure to yield the dosage form according to the invention with preceding, simultaneous or subsequent exposure to heat.”). Indeed, subsequent heat is discussed a total of five times in the patent, including in one of the patent claims *See* Claim 25; ’060 Patent at 23:9. However, in an example using the subsequent application of heat, the specification inexplicably states that, “in direct tableting with subsequent exposure to heat, the formed tablets are briefly heated at least to the softening temperature (glass transition temperature, melting temperature; sintering temperature) of component (C) and

cooled again.” ’060 Patent at 11:33–36 (emphasis added). The use of the words “cooled again” is baffling. If the thermoforming process encompasses the *subsequent* application of heat, how can the tablets be “cooled again”? This would imply that the tablets had been heated and cooled at some previous point rather than subsequently. Indeed, as defendants point out, Trial Tr. at 1095:14–15, none of the examples tested in the ’060 Patent actually used the subsequent application of heat. *See* ’060 Patent at 17–20.

The court concludes that the singular and baffling use of “cooled again” in column 11 of the ’060 Patent would be insufficient to cause a person of ordinary skill in the art to exclude subsequent heat from his understanding of the term “thermoformed,” given that the specification and one claim expressly allow for the subsequent application of heat.

Nor is there anything in the prosecution history of the ’060 Patent to suggest the inventors had, at some point after filing the patent application, disclaimed a reading of thermoforming inclusive of the subsequent application of heat. At trial, defense counsel attempted to establish that Grünenthal had made statements to the Patent and Trademark Office removing subsequent heat from the definition of thermoforming. Trial Tr. at 1091:3–7. However, these statements were made in the prosecution of a different patent, not the ’060 Patent. *See* November 27, 2006 Response to Office Action from Certified Prosecution History for U.S. Patent No. 8,114,383 (PTX-30B at 1). To the extent these statements are relevant to the ’060 Patent, Grünenthal merely said “the inventive dosage forms exhibiting the desired properties may be obtained only if,

during preparation of the dosage form, the components are exposed to a sufficient pressure at a *sufficient temperature* for a sufficient period of time.” See November 27, 2006 Response to Office Action from Certified Prosecution History for U.S. Patent No. 8,114,383 (PTX-30B at 11) (emphasis added).

As defendants suggest, “during preparation” could be read to mean “during an early” stage of the manufacturing process of the dosage form. However, when read in context, “preparation of the dosage form” does not refer to some early stage in the manufacturing process of the tablets, but to the manufacture of the tablets as a whole. See *id.* Thus, the statement to the PTO merely provided that during the manufacture of the dosage form, the components are exposed to heat. This squares completely with a definition of “thermoformed” encompassing the subsequent application of heat.

For these reasons, the court construes the terms “thermoformed dosage form” to mean “a dosage form created by applying pressure to a mixture of the active ingredient and high-molecular weight polymer and by applying the prior, simultaneous, or subsequent application of heat.”

iii. The Term “Breaking” Means the Separation of the Dosage Form Into Two or More Pieces.

Claim 1 of the '060 Patent provides that the dosage form will “exhibit[] a breaking strength of at least 500 N.” '060 Patent at 21:13–15. Breaking strength is the primary feature of invention. See *id.* at 2:26–30. The invention is intended to create dosage forms which are hard enough to withstand 500 newtons of force, a level of pressure so high that it would be exceedingly difficult to crush the

dosage form using household tools. *Id.* at 2:38–42.

At trial, the parties advanced different constructions of the term “breaking.” No party disputed that a dosage form may deform and still be unbroken. *See, e.g.*, Trial Tr. at 2173:3–5. But plaintiffs argued that in order for a dosage form to “break,” it must separate into two or more pieces. Trial Tr. at 1177:8–9. Defendants argued that “breaking” occurs earlier, when the dosage form cracks or “fractures.” *See, e.g., id.* at 1178:5–10. These competing constructions are relevant to infringement—if defendants’ tablets “break” before 500N of force is applied, then they do not infringe the hardness claims of the ’060 Patent.

Defendants’ construction is at odds with the specification. The specification contemplates scenarios where the tablets deform, but explains that deformation is not tantamount to breaking. *Id.* at 17:24–26. Moreover, defendants’ construction overlooks large sections of the specification describing the invention as a means for preventing comminution or *pulverization* of the dosage form. This prevention of crushing (and by extension the prevention of snorting and injecting) is the dominant theme of the specification. *See id.* at 2:26–39. When a tablet is crushed, it separates into two or more pieces, and then hundreds of pieces, which can then be snorted and injected. Thus, to be abused, the tablet *must* separate into multiple pieces. *See* ’060 Patent at 1:33–35. By the same token, to be abuse-proofed, the tablet resists separation into multiple pieces when exposed to mechanical forces below 500N. *Id.* at 2:37–42. Defendants’ construction of “breaking” is inconsistent with this language. A

tablet that is cracked or fractured, but not separated into multiple pieces, is useless to the abuser for snorting and injecting.

A person of ordinary skill in the art, upon reading the specification, would understand that where it describes tablets with high breaking strength, it means tablets that will not separate into multiple pieces before 500N of force is applied. The court construes the limitation “exhibits a breaking strength of at least 500 N” to mean “only separates into two or more pieces when exposed to a force of at least 500 newtons.”

Some additional terms of Claim 1 were not disputed at trial, but require construction to be fully understood. An ingredient with “abuse potential” is one susceptible to abuse, especially opiates and opioids, which are misused to obtain a euphoric state. ’060 Patent at 1:25–32. Where the claim calls for “physiologically acceptable auxiliary substances,” a person of ordinary skill in the art would understand this to mean a substance intended to further reduce abuse. See ’060 Patent at 6:30–35.

In light of the above considerations, the court construes Claim 1 to read as follows:

“A dosage form that reduces the potential for abuse which is formed by applying pressure and heat (before, during, or after pressure being applied) and comprising one or more active ingredients with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), at least one synthetic or natural polymer (C), wherein the polymer (C) has a molecular weight of at least 0.5 million according to rheological measurements, and optionally at least one wax (D), wherein the dosage form only separates into two or more pieces when exposed to a force of at least 500 newtons.”

Plaintiffs also assert Claim 4 of the ’060 Patent. Claim 4 depends from

Claim 1, and reads as follows:

4. A dosage form according to claim 1, Wherein the polymer (C) is at least one polymer selected from the group consisting of polyethylene oxide, polymethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers and the mixtures thereof.

'060 Patent at 21:19–24. This claim incorporates the limitations of Claim 1, but further recites that the polymer used be selected from a group of certain polymers including polyethylene oxide and others.

Claim 9 of the '060 Patent also depends from Claim 1, and reads as follows:

9. A dosage form according to claim 1, which additionally comprises at least one of the following components a)-f):

- (a) at least one substance which irritates the nasal passages and/or pharynx,
- (b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel optionally remains visually distinguishable when introduced into a further quantity of an aqueous liquid,
- (c) at least one antagonist for the active ingredient or active ingredients with abuse potential,
- (d) at least one emetic,
- (e) at least one dye as an aversive agent,
- (f) at least one bitter substance.

'060 Patent 21:37–52. Essentially, Claim 9 recites a dosage form which, in addition to meeting the limitations of Claim 1, also consists of at least one of six other barriers to abuse. *See id.* at 6:24–34. A substance that irritates the nasal passages or pharynx (part (a)) is one that brings about a strongly unpleasant physical reaction when administered via the nose or throat. *Id.* at 7:13–19. An “antagonist” (part (c)) is a substance in the dosage form which is inert when the dosage form is taken properly, but which blocks the effects of the active ingredient when the dosage form is subverted. *Cf. id.* at 9:35–67; *see also* Trial

Tr. at 985-86. An “emetic” (part (d)) is a substance that induces vomiting. A “dye as an aversive agent” (part (e)) is a dye of such brightness that it discourages abuse by injection into the vein. ’060 Patent at 10:45–47. A “bitter substance” (part (f)) is one that impairs flavor to discourage oral and nasal abuse. *Id.* at 10:54–58.

iv. The Viscosity Increasing Agent Must Be Distinct From the Hardening Polymer.

As discussed, Claim 9 describes six barriers to abuse beyond the hardening feature of Claim 1. Part (b) of Claim 9 provides that the dosage form will include “at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form” ’060 Patent at 21:41–45.

The definition of “viscosity-increasing agent” was never seriously disputed at trial.³ What was disputed, however, is whether the viscosity-increasing agent of Claim 9 must be distinct from the hardening polymer of Claim 1. *See, e.g.*, Trial Tr. at 1044. As discussed, Claim 1 of the ’060 Patent requires the presence of a high-molecular weight polymer. *See* ’060 Patent at 21:9–11. It is this polymer which strengthens the tablet. *Id.* at 5:54–58. However, Claim 9 recites *additional* abuse-deterrent features beyond mere hardness. *See id.* at 21:37–51. One of

³ While not disputed, the specification leaves no doubt as to the meaning of “viscosity-increasing agent.” The specification explains that drug-abusers often attempt to subvert controlled-release drugs by crushing them and then mixing the resulting powder in a liquid which can be injected into the veins using a hypodermic needle. ’060 Patent at 8:27–38. A viscosity increasing agent is a substance that increases the thickness of the dosage form extract by forming a gel when exposed to a liquid. *See id.* at 8:39–45. A “gel” is simply an area of thicker consistency in the mixture of the extract and the surrounding aqueous liquid, one that preferably remains visually distinguishable. *See, e.g.*, ’060 Patent at 8:19–27.

these additional barriers is the use of a viscosity-increasing agent that forms a gel. The purpose of the gel is simple. It makes a tablet that has been cut and mixed with water difficult to inject intravenously. *Id.* at 8:27–38. Plaintiff Grünenthal suggests that the hardening polymer of Claim 1 can also qualify as the viscosity increasing agent of Claim 9(b). Defendants argue the opposite, that the viscosity-increasing agent must be distinct from the hardening polymer.

Defendants have the correct reading of Claim 9. Claim 9 provides that the dosage form of Claim 1 will “*additionally* comprise[]” one of the six other abuse deterrent features, one of which is a viscosity-increasing agent. ’060 Patent at 21:37–38 (emphasis added). A person of ordinary skill in the art, upon reading the words “*additionally* comprising,” would understand that the viscosity increasing agent is distinct from (in “*addition*” to) the hardening polymer of Claim 1. A contrary reading would render the words “*additionally* comprising” meaningless.

Defendants’ construction is also supported by the specification examples. The specification lists six examples of dosage forms created according to the invention. Each of these dosage forms was subjected to various tests. The dosage forms in the first three examples contained no separate viscosity-increasing agent, but simply the hardening polymer polyethylene oxide. *See* ’060 Patent at 17–18. These dosage forms were only tested for *hardness*, and were not tested for producing a gel. *Id.* On the other hand, the dosage forms from examples 4, 5, and 6 did contain a separate viscosity increasing agent, xanthan gum. *See* ’060 Patent at 19–20. These dosage forms were tested for hardness *and* for their

gelling properties. See '060 Patent at 19–20. Each of them, when cut into multiple pieces and mixed with water, formed a “highly viscous gel.” *E.g.*, *id.* at 20:19. The inventors’ decision to test only the examples with a separate viscosity-increasing agent for gelling indicates their understanding that the hardening polymer would be distinct from the viscosity-increasing agent. This would be apparent to a person of ordinary skill in the art comparing examples 1–3 with examples 4–6.

Thus, in light of the language of the claims and the examples of the specification, the court adopts defendants’ construction of “viscosity-increasing agent” as requiring a substance distinct from the hardening polymer. The entirety of part (b) of Claim 9 would read as requiring a distinct viscosity-increasing agent which, with an aqueous liquid, forms a gel that preferably remains visible when introduced into a further quantity of aqueous liquid.

Claims 22 and 23 of the '060 Patent depend from Claim 1, and read as follows:

22. A dosage form according to claim 1, which comprises at least one active ingredient at least partially in controlled release form.

23. A dosage form according to claim 22, wherein each of the active ingredients with abuse potential (A) is present in a controlled release matrix.

'060 Patent at 22:59–64.

Upon reading the specification, a person of ordinary skill in the art would understand that a “controlled release” dosage form is one that releases its active ingredient slowly over time. See '060 patent at 45–49. A “controlled release matrix,” as used in the '060 Patent, may consist of hydrophilic gel-forming

materials which swell and release the active ingredient by diffusion. *Id.* at 17:20–25. The controlled release matrix may also consist of hydrophobic (water-hating) materials which release the active ingredient through pores in the matrix. *Id.* at 16:23–25.

Claim 24 depends from Claim 23, and reads as follows:

24. A dosage form according to claim 23, wherein component (C) and/or component (D) also serve as a controlled release matrix material.

'060 Patent at 22:65–67. This claim ultimately traces back to Claim 1, which, as discussed, has four components: (A), (B), (C), and (D). Claim 24 simply provides that the synthetic or natural polymer (C) and/or the optional wax (D) may also serve as the controlled release matrix material. See '060 Patent at 21:5–15; 22:65–67.

Claim 25 of the '060 Patent is a process claim. See '060 Patent at 23:1. Claim 27 is a product claim covering the dosage form obtained by the process according to Claim 25. *Id.* at 11–15. Together, claims 25 and 27 read as follows:

25. A process for the production of a dosage form according to claim 1, comprising:
 mixing components (A), (B), (C) and the optionally present component (D) and the optionally present components (a) to (f) to form a resultant mixture, and
 press-forming the resultant mixture, optionally after granulation, to yield the dosage form with preceding, simultaneous, or subsequent exposure to heat.

27. A dosage form obtainable by a process according to claim 25.

'060 Patent at 23:1–14. These claims are novel in that they refer to a process known as “press-forming.” Press-forming means exactly what it sounds like: the

dosage form is created by putting the mixture in a press, with heat applied before, during, or after pressure is applied in the press. See '060 Patent at 11:13–19; 23:3–9. Thus, Claim 25 refers to a process of creating a dosage form using a press and the application of heat; and Claim 27 refers to the actual dosage form created as a result of that process.

Claims 28 and 29 of the '060 Patent reads as follows:

28. A method of treating a therapeutic condition in a patient suffering therefrom, said method comprising administering to said patient a dosage form according to claim 1.

29. The method according to claim 28, wherein the therapeutic condition is pain.

'060 Patent at 23:13–19. The term “therapeutic condition” is not defined in the patent, but would be understood as meaning a condition requiring medical treatment. Thus, Claim 28 is construed as a method claim requiring the dosage form of Claim 1 to be administered to a patient suffering from a condition requiring medical treatment. Claim 29 is identical, except that it requires the condition requiring medical treatment to be pain. *Id.* at 23:17–19.

Claims 30, 31, 32, and 33 depend from Claim 1. These claims read as follows:

30. A dosage form according to claim 1, wherein the polymer (C) is polyethylene oxide having a molecular weight of from 1-15 million g/mol.

31. A dosage form according to claim 1, wherein the one or more active ingredients with abuse potential (A) is/are selected from the group consisting of oxymorphone, oxycodone, tapentadol and the physiologically acceptable salts thereof.

32. A dosage form according to claim 31, which is in the form of a

tablet.

33. A dosage form according to claim 1, wherein the content of polymer (C) is at least 60% by weight relative to the total weight of the dosage form.

'060 Patent at 23:18–24:10. Claim 30 simply repeats the dosage form of Claim 1, but provides that the polymer used will be polyethylene oxide (“PEO”) with a molecular weight, or mass, of 1-15 million grams per mole. *See id.* 23:18–20. Similarly, Claim 31 requires that the active ingredient with abuse potential be oxymorphone, oxycodone, tapentadol or the salts thereof. *Id.* at 24:1–5. Claim 32 provides that the dosage form will be a tablet. Finally, Claim 33 provides that the polymer used in Claim 1 will comprise at least 60% of the total dosage form. *Id.* at 24:8–10.

Claim 34 of the '060 Patent also depends from Claim 1, and reads as follows:

34. A dosage form according to claim 1, which is in the form of a tablet, wherein the one or more active ingredients with abuse potential (A) is/are selected from the group consisting of oxymorphone, oxycodone, tapentadol and the physiologically acceptable salts thereof; Wherein the polymer (C) is polyethylene oxide having a molecular Weight of from 1-15 million g/mol:
and wherein the content of polymer (C) is at least 30%⁴ by Weight relative to the total weight of the dosage form.

'060 Patent at 24:11–19. This claim recites the dosage form according to Claim 1, but specifies that component (A) will be oxymorphone, oxycodone, or tapentadol or their salts; and that component (C) will be PEO with a mass of between 1–15 million grams per mole and will comprise 60% of the weight of the

⁴ This value, 30%, was later corrected to read 60%.

dosage form.

2. Step Two: Infringement.

Having construed the claims of the '122, '216, and '060 patents, the next step is to determine whether defendants' pharmaceutical products, if manufactured and sold,⁵ would infringe on those claims.

Direct infringement exists if the defendants' product or methods, as described in their ANDAs, meet each and every element of the claims. *Sunovian Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013). If the defendants' products or methods fail to meet an element of the claims asserted, they may still infringe under the "doctrine of equivalents" if the differences are insubstantial. *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1167 (Fed. Cir. 2012). To determine if the differences are insubstantial, the court employs the "function, way, and result" test. The missing element is insubstantial if the accused product performs substantially the same *function*, in substantially the same *way*, and achieves substantially the same *result* as each claim limitation in the asserted patent. *Id.*

Indirect infringement occurs where a defendant, rather than directly infringe the patent, induces another party to do so. *See* 35 U.S.C. § 271 (b). A person infringes by inducement when he "actively and knowingly aid[s] and abet[s] another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Systems, Inc.*, 911 F.2d 670, 675 (Fed. Cir. 1990). This requires a showing that the defendant knew of the patent, knowingly induced direct infringement of the

⁵ Defendant Actavis is already to market with its generic product.

patent by a third party, and did so with the specific intention that the third party directly infringe the patent. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1328 (Fed. Cir. 2009); *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). In ANDA litigation, evidence of an intent to induce infringement of a method claim may be found if the defendant's proposed product label instructs users to perform the patented method. See *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010).

The requirement that the defendant induce a third party to *directly infringe* the patent raises difficulties with regard to method claims. A method claim consists of multiple steps. *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S. Ct. 2111, 2117 (2014). Of course, if the defendant itself performs all of these steps, it will be responsible for direct infringement. Likewise, if the defendant induces a third party to perform all of these steps, that third party will have committed direct infringement, and the defendant will be liable for inducing that direct infringement. Cf. *id.* A more difficult scenario is presented where a defendant induces the third party to perform some, but not all, of the steps of the method claim. In such cases, how may the defendant be liable for inducing infringement of the method claim when all of the steps of the method claim have not been performed? The answer, as the Supreme Court recently decided in *Limelight*, is that there can be no indirect infringement unless the defendant induces the third party, a single actor, to perform all of the steps provided. *Id.* at 2119 (“[A] method patent is not directly infringed . . . unless a single actor can be held responsible for the performance of all steps of the patent.”).

Finally, a defendant may also commit contributory infringement. Contributory infringement occurs when a defendant makes a component he knows will be used by others to make an infringing product or to conduct an infringing method. See 35 U.S.C. § 271(c). To prove contributory infringement of a method claim, the plaintiff must show that: “there is direct infringement; the accused infringer [the defendant] had knowledge of the patent at issue; the component has no substantial non-infringing uses; and the component is a material part of the invention.” *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010) (internal numbering omitted).

a. Infringement With Regard to the '122 and '216 Patents.

As demonstrated in the claim construction section of this decision, Endo asserted an unusually large number of claims in these actions. Endo asserted four claims⁶ with regard to the '122 Patent; and sixteen claims⁷ with regard to the '216 Patent. This large number of claims is not as unwieldy as it may seem, however, because most of the claims repeat common elements. More significantly, defendants do not dispute infringement of most of the asserted claims. In stipulations dated March 27, 2015 and April 9, 2015, defendants agreed that their tablets “satisfy each limitation of each '122 and '216 patent claim asserted against them” except with regard to two issues: (i) whether their tablets satisfy the “food effect limitations” of the asserted claims; and (ii) whether

⁶ Claims 2, 3, 19, and 20.

⁷ Claims 1, 22, 40, 42, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, 82 (not all claims asserted against all defendants).

defendants infringe the asserted method claims. *See* Stipulation and Order at 1, No. 12-CV-8060 (Mar. 27, 2015) (Dkt. #152); *see also* Second Stipulation and Order at 1, No. 12-CV-8060 (Apr. 9, 2015) (Dkt. # 154).

i. Whether Defendants' Tablets Satisfy the Food Effect Limitations of the Asserted Claims of the '122 and '216 Patents.

Defendants argue that their tablets do not satisfy the food effect limitations embodied in Claim 20 of the '122 Patent and claims 40, 42, 50, 54, 78, 80, and 82 of the '216 Patent. The "food effect" refers to a patient's physiological response to a drug after having eaten. For example, a patient who takes a drug with a pronounced food effect might experience much higher concentrations of the active ingredient if he has recently eaten. *See* Trial. Tr. at 298. Part of the invention claimed by Endo is a dosage form that addresses this "food effect," keeping the concentration of oxymorphone in the bloodstream at an acceptably constant rate regardless of whether a patient has eaten or has fasted. *See id.* at 299–300. Defendants argue that their tablets would not or do not infringe on the several food effect limitations of the '122 and '216 Patents.

Defendants infringe the food effect limitations of the '122 and '216 Patent if their tablets, upon being administered to a patient, produce the following effects: (1) the maximum observed concentration (C_{\max}) of oxymorphone in the bloodstream is at least 50% percent higher after having eaten a meal than it would be on an empty stomach; and (2) the subject exhibits total blood concentration levels ($AUC_{(0-\text{inf})}$) levels of oxymorphone no more than 20% higher after having eaten a meal as compared to having taken the dosage form on an

empty stomach.

At trial, Endo's expert on infringement, Dr. Reza Fassihi, testified that the defendants' submissions to the FDA prove that their drug products infringe or will infringe on the food effect limitations of the '122 and '216 Patents. Trial Tr. at 637:6. Dr. Fassihi explained that in order to obtain approval to sell a branded or generic drug, the FDA requires an applicant to demonstrate the drug's food effect, if any. *Id.* at 641. In the case of a new branded drug, the applicant performs food-effect studies, which measure the effect of the drug in groups of human subjects who have been fed or who have fasted. *See id.* at 638:10–19. The resulting data will demonstrate to the FDA whether a food effect exists. On the other hand, a generic drug applicant seeking FDA approval is not required to perform new food effect studies. *Id.* at 641. Rather, the generic manufacturer may submit to the FDA information showing that their proposed drug will have the same effects as the branded drug. *Id.* This is the course each of the defendants chose. Based on the information defendants provided to the FDA, Dr. Fassihi concluded that their generic products infringe or will infringe on the food effect limitations of the asserted patent claims.

In reaching his conclusion, Dr. Fassihi relied heavily on defendants' "package inserts." A package insert is included with the drug, and provides information to patients and doctors on how to correctly take and prescribe the tablets. *Id.* at 643:15–20. Defendants' package inserts expressly state that their products satisfy the AUC and C_{\max} limitations of the '122 and '216 patents. *See, e.g.,* Actavis CRF Package Insert (PTX-2436 at 21) (" C_{\max} was increased by

approximately 50% in fed subjects compared to fasted subjects The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects.); *see also* Roxane Package Insert (PTX-3070 at 4). Each of defendants' package inserts contains this information. Trial Tr. at 647:16-18 ("Every defendant has the same feed-effect information and package insert for the pills that they have made.").

Dr. Fassihi also relied on defendants' statements to the FDA that their proposed generic drugs are bioequivalent to Endo's branded drugs. *See* Trial Tr. at 717. Each defendant conducted bioequivalence studies to show that their drug does not differ significantly from Endo's branded drugs. *See, e.g.*, Actavis Bioequivalence Study (PTX-2385). This is important because Endo, in drafting the '122 and '216 Patents, recited limitations reflecting their extensive clinical and laboratory testing of dosage forms that would become OPANA[®]ER. Indeed, the asserted claims of the patents, including the food effect claims, are drawn around studies Endo performed during the testing and development of the branded product. *See* Trial Tr. at 482. For example, one of Endo's studies, highlighted in the specifications of the patents, showed an oxymorphone peak concentration level (C_{max}) 58% higher under fed conditions as compared to fasted conditions. *See, e.g.*, '216 Patent at 17:43–46. The relevant patent claim, then, called for a C_{max} greater than 50% under fed conditions as compared to fasted conditions. *See, e.g.*, '216 Patent at 30:3–5.

Dr. Fassihi reasoned that defendants, by demonstrating to the FDA that their products are bioequivalent to OPANA[®]ER and OPANA[®]ER CRF, also

demonstrated that their products exhibit the same food effects as those branded drugs. Trial Tr. at 717. The court finds him to be persuasive in explaining this inference. The bioequivalence of the products described in defendants' ANDAs indicates that those products will exhibit the same pharmacokinetic properties as Endo's branded drug, the effects of which are embodied in relevant claims of '122 and '216 Patents.⁸ Trial Tr. at 716. The court need not rely solely on this inference, however. As discussed, Dr. Fassihi referred to defendants' package inserts in reaching his conclusions on infringement. He also considered defendants' product labels, dissolution test data, requests for bio-waivers, approval letters, and other evidence. See Trial Tr. at 654–55.

On cross-examination, defendants argued that Dr. Fassihi should have performed his own food effect studies of defendants' products to determine infringement, rather than rely on their submissions to the FDA. Trial Tr. at 722–724. Having heard Dr. Fassihi's testimony, the court concludes that such independent testing was unnecessary. Dr. Fassihi's review of Defendant's ANDA submissions, including defendants' package labels and other documentation, revealed sufficient evidence of infringement to meet plaintiffs' burden. To require plaintiffs to perform independent clinical testing of each of defendants products would put them to a burden beyond a preponderance of the evidence.

The court concludes, upon hearing the credible testimony of Dr. Fassihi, and upon reviewing the documents he relied on, that it is more likely than not

⁸ Another of Endo's experts, Dr. Stephen Ogenstad, used statistical methods to show that Endo's product, OPANA®ER in both crushable and non-crushable formulations, actually satisfies the limitations of the asserted claims. See Trial Tr. at 2089–92.

that defendants' generic drug products, as described in their ANDAs, would satisfy the food effect limitations of the asserted claims of the '122 and '216 patents.

ii. Whether Defendants Infringe the Asserted Method Claims of the '122 and '216 Patents.

Defendants argue that they do not infringe the asserted method claims of the '122 and '216 Patents. With regard to direct infringement, defendants argue that they do not directly infringe the claims because they simply make and sell tablets and do not actually administer them to patients. *See* Trial Tr. at 613:18 ("We just manufacture pills . . . we don't ever administer the pill to the patient."). With regard to indirect infringement, defendants argue that: (1) their product labels do not instruct subjects to take the tablets under fed *and* fasted conditions, thus defendants do not induce infringement of the method claims that have food effect components; and (2) no single person performs all of the steps of the asserted method claims, and since there is no direct infringement by any single person, there can be no indirect infringement Trial. Tr. at 530:12–13 (referring to the Supreme Court's decision in *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S. Ct. 2111 (2014)).

Defendants are correct in that they, as drug manufacturers, do not directly infringe the asserted method claims of '122 and '216 Patents. Defendants do not feed tablets to patients or subjects, and thus do not "administer" them as required in Claim 20 of the '122 Patent, as required in part (b) of Claim 38 of the '216 Patent (and the asserted claims, claims 40 and 42, that depend from it), and as required by Claim 82 of the '216 Patent. Thus, defendants cannot be

liable for direct infringement.

With regard to indirect infringement, defendants are incorrect to argue that they must instruct patients to take their tablets under fed and fasted conditions.

Defendants have submitted to the FDA proposed product labels for their generic oxymorphone products. See Trial Tr. at 517:1–4. These product labels instruct patients to take the generic tablets on an empty stomach. See, e.g., DTX 3542 at 2244. At trial, defendants’ expert on non-infringement, Dr. Timothy Deer, testified that in prescribing generic oxymorphone tablets to patients, he and his colleagues are careful to instruct them according to the product labels. Trial Tr. at 517:1–14. Thus, defendants argue that since their labels do not instruct patients to take the tablets under fed conditions, they do not induce infringement of the “food effect” portions of the asserted method claims.

This argument relies on an unsupported reading of the asserted method claims. The most complicated of the method claims, claims 40 and 42 of the ’216 Patent (both of which depend from Claim 38), consist of two parts and require that the tablets be provided to the subject, and then administered to that subject.⁹ See ’216 Patent at 29:49–30:40 (“A method for treating pain in a human subject . . . comprising the steps of: (a) providing a solid oral dosage form . . . and (b) administering a single dose . . . to the subject . . .”). The claims then go further, stating that the composition that was administered, *upon being tested*,

⁹ The other asserted method claims, Claim 20 of the ’122 Patent and Claim 82 of the ’216 Patent, do not require that the tablet first be “provided” to the subject. See, e.g., ’216 Patent at 34:56–60. They merely require administration of the tablet. *Id.*

will exhibit certain *in vitro* and *in vivo* characteristics. *See, e.g., id.* at 29:51–67. (“Wherein upon placement of the composition in an *in vitro* dissolution test comprising”). Similarly, Claim 20 of the ’122 provides that upon oral administration of the tablet, the subject will exhibit higher blood concentrations of oxymorphone if he has eaten than if he had taken the tablet on an empty stomach. ’122 Patent at 1–5.

This language indicates that it is not necessary to the completion of the methods that the tablet be taken under fed *and* fasted conditions. Rather, the methods are completed once the tablets are administered. Once the tablets are administered, the subject will exhibit different pharmacokinetic effects depending on whether he has eaten or fasted. *See, e.g.,* ’216 Patent at 15–28; *see also* ’122 Patent at 1–5. It is the taking of the qualifying tablet (one that will produce the claimed pharmacokinetic effects) that constitutes the method claimed. Once a patient administers the qualifying tablet, he directly infringes the method claims.

Thus, it is not necessary for defendants to instruct subjects to take the tablets under fed *and* fasted conditions. By instructing subjects to take the tablets at all, defendants assure that patients will complete the methods asserted in the ’122 and ’216 patents. Once patients have followed defendants’ instructions and infringed the method claims, their blood will exhibit certain pharmacokinetic characteristics. *See, e.g.,* ’216 Patent at 30:18–19 (“the dosage form provides detectable levels of 6-OH oxymorphone and oxymorphone.”). Those characteristics will be different if the patient has recently eaten. But the method

performed—the administration of the tablet—will be the same.

This puts to rest defendants’ argument regarding instruction, but the court must still resolve the question of whether a single actor performs all of the steps of the asserted method claims. As discussed, the Supreme Court has recognized that indirect infringement of a method claims requires proof of *direct infringement* by some third party. *Limelight*, 134 S. Ct. at 2117. But there can be no direct infringement by a third party unless that party has itself performed all of the required steps of the asserted method. *Id.* Thus, indirect infringement requires proof, by a preponderance of the evidence, that defendants induce a single party to perform all of the steps of the asserted method claims.

There is clear indirect infringement with regard to claims 20 of the ’122 Patent and 82 of the ’216 Patent. The methods recited in these claims is merely the administration of the dosage form to the subject. Defendants, through their product labels, instruct subjects to take qualifying generic oxymorphone tablets. *See, e.g.*, DTX-3542, DTX-3523; DTX-3563. In doing so, they demonstrate a specific intention to induce infringement. *See DSU Med. Cor. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006). The subjects then perform all of the steps of the methods recited in those claims, because they “administer,” or take orally, defendants’ tablets. *See* ’122 Patent at 26:54–56, 28:1–5; ’216 Patent at 34:56–60. Once the method is completed, the subjects’ blood will exhibit certain concentrations of oxymorphone depending on whether they have eaten or have fasted. ’122 Patent at 28:1–5. Thus, there is clear indirect infringement of claims 20 of the ’122 Patent and 82 of the ’216 Patent.

It is a closer question as to whether a single party performs all of the steps of claims 40 and 42 of the '216 Patent. As discussed, these claims require the tablet to be provided *and* administered to subjects. Dr. Deer, testified that multiple parties perform these two steps. As a prescribing physician, he performs the first step, providing the tablets, by making them available to patients. Trial Tr. at 522:15–25. This step is also performed when a pharmacy fills the prescription. *Id.* at 523:1–19. The second step, “administration,” occurs when the patient takes the pill orally. Thus, according to Dr. Deer, up to three parties are involved in performing the methods recited in claims 40 and 42 of the '216 Patent. Trial Tr. at 524:6–9 (“[A]t least three people are involved in this process, a physician, a pharmacy, and a patient.”). This would indicate that there can be no indirect infringement because no single party can be liable for direct infringement.

On the other hand, Endo’s expert on infringement, Dr. Fassihi explained that physicians and nurses in a hospital setting often perform both the “provide” and “administer” steps by directly giving patients tablets to swallow. *See* Trial Tr. at 656–57. This would imply that there is indirect infringement, since defendants induce a single party to perform the entire method claimed.

The court finds Dr. Deer to be more persuasive on this question. Defendants, through their product labels, instruct physicians to prescribe tablets to patients. By writing prescriptions for the tablets, physicians perform the first step of the methods recited in claims 38, 40, and 42 of the '216 Patent by making tablets available to patients. However, in the majority of cases, it is

the patient who performs the second step and administers the tablet at home to treat chronic pain. While there may be isolated settings where physicians physically insert tablets into patients' mouths, *see* Trial Tr. at 657:1–7, plaintiffs did not provide the court with sufficient evidence to find that this happens with any degree of regularity. Thus, plaintiffs have not shown that it is probable that a single actor performs all of the steps of the methods recited in claims 40 and 42 of the '216 Patent, and there is no direct infringement of those claims. Since there is no direct infringement, defendants cannot be liable for indirect infringement of claims 40 and 42.

For similar reasons, contributory infringement is also unavailing with regard to claims 40 and 42 of the '216 Patent. While Endo has satisfied most of the elements of its contributory infringement claim (by showing no-substantial non-infringing use; knowledge, and materiality); *see* Trial Tr. at 668, it did not show that there is direct infringement of the methods recited in claims 40 and 42. Again, Endo has not submitted sufficient evidence showing that any third party directly infringes the method of claims 40 and 42 of the '216 Patent by both "providing" and "administering" the dosage form to subjects. Thus, without direct infringement, there can be no contributory infringement. *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 483 (1964) ("There can be no contributory infringement in the absence of a direct infringement.").

The court makes the following conclusions with regard to infringement of the '122 and '216 patents. The court concludes that plaintiffs have satisfied their burden in showing that defendants' generic drug products, as described in their

ANDAs, infringe the food effect limitations of the asserted claims. The court concludes that defendants indirectly infringe method claims 20 of the '122 Patent and 82 of the '216 Patent. However, the court concludes that plaintiffs have failed to satisfy their burden and show indirect infringement of claims 40 and 42 of the '216 Patent. Thus, defendants infringe all of the asserted claims except those two.¹⁰

b. Infringement With Regard to the '060 Patent.

Grünenthal presented evidence of infringement of the '060 Patent against Actavis, Impax, ThoRx and Teva.

As discussed above, the '060 Patent is the product of Grünenthal's efforts to produce a tablet so hard that it is resistant to abuse through crushing, and which also accommodates other barriers to abuse. As with the '122 and '216 patents, plaintiffs have asserted an unusually large number of claims of the '060 patent. However, determining infringement of these claims is straightforward, involving five issues. These issues are whether defendants' tablets: (i) are abuse-

¹⁰ To be specific, through their stipulations and the court's findings, each of the defendants infringes claims 2, 3, 19, and 20 of the '122 Patent. Through their stipulations and the court's findings, the following conclusions apply with regard to the '216 Patent. Defendant Actavis, in case No. 13-cv-436, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant Amneal, in case No. 12-cv-8115, is liable for infringement of claims 1, 22, 50, 54, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant ThoRx, in case No. 12-cv-8317, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant Impax, in case No. 13-cv-435, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, and 71 of the '216 Patent. Defendant Teva, in case No. 12-cv-8060, is liable for infringement of claims 1, 22, 50, 54, 62, 64, 71, 73, 74, 78, 79, 80 and 82 of the '216 Patent. Defendant Sun Pharmaceuticals, in case No. 13-cv-8597, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 Patent. Defendant Actavis, in case No. 12-cv-8985, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 80, and 82 of the '216 Patent. Defendant Roxane, in case No. 13-cv-3288, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 Patent. Defendant Sun Pharma, in case No. 13-cv-4343, is liable for infringement of claims 1, 22, 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, and 82 of the '216 Patent.

proofed; (ii) are “thermoformed”; (iii) have a breaking strength of at least 500 newtons; (iv) have a “viscosity-increasing agent” which “forms a gel” with the extract obtained from the dosage form; and (v) whether plaintiffs have shown infringement of the remainder of the asserted claims.

i. Whether Defendants’ Tablets Are Abuse-Proofed.

Claim 1 of the ’060 Patent describes a dosage form that is “abuse-proofed.” See ’060 Patent at 21:6. The portions of the trial dealing with this limitation focused primarily on issues of claim construction, specifically, whether “abuse-proofed” requires a demonstrated elimination of abuse, or whether it simply requires a reduction in the potential for abuse. See, e.g., Trial Tr. at 1137:7–11. As the court determined in the claim construction section of this decision, a person of ordinary skill in the art would understand the term “abuse-proofed” as merely requiring a reduction in the potential for abuse. See *supra* Part A(1)(c)(i).

At trial, defendant Actavis was the only party to dispute whether its tablets are “abuse-proofed.” Trial Tr. at 1137:4. During his direct testimony, defendants’ expert on non-infringement, Dr. Muzzio, stated that the issue regarding “abuse-proofed” was not that it required a complete eradication of all abuse, but that it required some factual showing that a tablet achieves a significant elimination of abuse. Trial Tr. at 2151–52. Dr. Muzzio testified that plaintiffs have failed to show that defendants’ tablets actually cause a significant elimination of abuse, and thus have failed to meet their burden in showing infringement. *Id.*

Plaintiffs have met and exceeded their burden of showing that defendants’ tablets reduce the potential for abuse. As will be discussed below, plaintiffs’

expert, Dr. Stanley Davis, tested defendants' generic products and showed that they exhibit an exceptionally high breaking strength. *See infra* Part A(2)(b)(iii). Dr. Davis explained that the hardness of defendants' tablets reduces their potential for abuse by making it more difficult to grind the dosage form into a powder suitable for snorting and injecting. Trial Tr. at 1150:18–22. This is not mere speculation. Indeed, in Actavis's submissions to the FDA, it repeatedly refers to its generic product as "crush-resistant." *See, e.g.*, PTX 2369¹¹. at 3970. When Actavis tested its tablets using a mortar and pestle, they flattened into a "pancake" shape but did not crumble into a powder. *Id.* ("Both crushed tablets resembled a pancake.").

In the court's view, it is absurd to argue that a crush-resistant tablet fails to reduce the potential for abuse to some extent. Of course, a drug abuser who fails to crush a hard tablet may take other efforts to subvert the tamper-resistant properties of the drug. *See, e.g.*, Letter from the FDA to Robert Bart (May 10, 2014) at 5 (DTX 5032) ("[E]xtended-release features can be compromised . . . when subjected to other forms of manipulation . . ."). But this does nothing to diminish the fact that the tablet reduces the potential for abuse of the dosage form by crushing.

A crush-resistant tablet reduces the potential for abuse through crushing, and is thus "abuse-proofed." Having heard the testimony of Dr. Davis, *see infra*

¹¹ Actavis objects to the admission of this exhibit, claiming it was "never discussed by any witness." That objection is overruled. Plaintiffs' expert, Dr. Davis, relied on the exhibit during his direct testimony. *See* Trial Tr. at 1209, and the court rules that it is relevant and not otherwise inadmissible. *See* Fed. R. Evid. 402.

Part A(2)(b)(iii), and Dr. Muzzio, and upon reviewing the exhibits they relied on, the court is satisfied that defendants' generic products are "abuse-proofed" as required by Claim 1 of the '060 Patent.

ii. Whether Defendants' Tablets are Thermoformed.

Each of the asserted claims of the '060 Patent require a "thermoformed dosage form." *See, e.g.*, '060 Patent at 21:6. As determined in the claim construction section of this decision, a "thermoformed dosage form" is a "dosage form created by applying pressure to a mixture of the active ingredient and high-molecular weight polymer and applying the prior, simultaneous, or subsequent application of heat." *See supra* Part A(1)(c)(ii).

Defendants' ANDAs describe the process used in manufacturing their generic oxymorphone tablets. Defendant Actavis uses a fixed-speed blender to mix oxymorphone hydrochloride with the hardening polymer. *See* Trial Tr. at 1170, *see also* PTX-2372¹² at 24645. It then compresses the mixture in a rotary tablet press with a force feeder. PTX-2372 at 24645. Actavis cures the mixture by applying 65–72°C of heat. *Id.* at 24649. [REDACTED]

[REDACTED] PTX-2766 at 0389; PTX-3413 at 0415. Teva's manufacturing process involves first blending the ingredients, and then compressing the mixture in a tablet press. *See* PTX-3257 at 0399. Teva

¹² Actavis objects to the admission of this exhibit, claiming it was "never discussed by any witness." That objection is overruled. Plaintiffs' expert, Dr. Davis, relied on the exhibit during his direct testimony. *See* Trial Tr. at 1169, and the court rules that it is relevant and not otherwise inadmissible. *See* Fed. R. Evid. 402.

then heats the compressed mixture for 15–90 minutes, and coats them. See PTX-3257 at 0399.

The court concludes that because thermoforming encompasses manufacturing processes involving the subsequent application of heat, each of the defendants' tablets are "thermoformed" as required by Claim 1 of the '060 Patent.

iii. Whether Defendants' Tablets Have a Breaking Strength of at Least 500N.

Defendants argue that their generic oxymorphone tablets do not have a breaking strength of at least 500N, and therefore do not infringe any of the asserted claims of the '060 Patent. See, e.g., Trial. Tr. at 151–53.

As discussed in the claim construction portion of this decision, a tablet is "broken" when it separates into two or more pieces. See *supra* Part A(1)(c)(iii). Thus, to satisfy its burden on infringement, Grünenthal must prove by a preponderance of the evidence that defendants' tablets are unbroken, or not separated into two or more pieces, when subjected to a pressure of at least 500N.

Dr. Davis tested each of defendants' tablets to determine whether they broke when subjected to pressures of at least 500N. See Trial Tr. at 1185. He used a sophisticated protocol in doing so. Using a calibrated Instron testing device, Dr. Davis took ten of each dosage strength of defendants' tablets and applied 503 newtons of force to them. See Trial Tr. at 1279:9–11. After being squeezed by the Instron testing device, Dr. Davis's assistant removed the tablets and placed them onto a "data form," or a sheet of paper with labels identifying

the tablets. *Trial Tr.* at 1191–92. Dr. Davis then took photographs of all of the tablets. Upon studying these photographs, Dr. Davis observed that while some of the tablets had deformed, none of them had broken into two or more pieces. *Trial Tr.* at 1192:22–24.

Dr. Davis also created “compression curves” of defendants’ tablets, showing the extent to which the tablets compressed, or flattened, when subjected to pressures between zero and 504 newtons. *See, e.g.*, PTX 2567. Based on his observations, Dr. Davis concluded that defendants’ tablets are sufficiently hard as to infringe the breaking strength limitation of Claim 1 of the ’060 Patent. *Trial Tr.* at 1194.

Dr. Muzzio reviewed Dr. Davis’s photographs, and with regard to defendant Actavis, concluded that some of the tablets had, in fact, separated into two or more pieces upon being tested at 503N. *Trial Tr.* at 2122:2–3 (“If anything, these pictures show broken tablets. You see dust and pieces falling off.”). Dr. Muzzio also reviewed Dr. Davis’s compression curves. *Trial Tr.* at 2122–23. He interpreted the compression curves as showing that that defendants’ tablets “break” before 500N because at some point they continue to flatten without requiring the application of additional force. *See Trial Tr.* at 2123:9–19.

Defendants also argued that rather than simply rely on Dr. Davis’s photographs of the tablets, those tablets should have been brought to court so the court could make the factual determination of whether they are broken. *See Letter from Charles Weiss to the Court* at 2 (Feb. 25, 2015); No. 13-CV-436 (ECF #75). The court initially agreed, stating “It would be helpful to the court, as the

finder of fact, for the tablets to be available at trial if needed in either party's presentation." Order of Mar. 19, 2015, No. 13-CV-436 (ECF #118). However, as trial approached, Grünenthal found it impossible to secure release of the tablets from the facility in which they were stored, given that they are a controlled substance. *See* Letter from Jennifer Roscetti to the Court at 3 (Mar. 9, 2015), No. 13-CV-436 (ECF #94) ("Actavis feigns ignorance as to the legal burdens of handling and transporting a Schedule II controlled substance pursuant to the Controlled Substances Act . . ."). Given Grünenthal's concerns, the court settled on an intermediate solution, allowing Actavis to travel to Grünenthal's expert's testing facility in Pennsylvania to make its own inspection of the tablets. *See* Trial Tr. at 229–230. The court then instructed Grünenthal that it need not produce the actual tablets at trial. Trial Tr. at 230:3–5 ("If you can [produce the tablets], fine. If you can't [produce them], we'll do without.").

In the end, having heard the testimony of Dr. Davis and Dr. Muzzio, and having examined photographs of the tablets taken both when they were tested and on the eve of trial,¹³ the court finds that defendants' tablets, in every dosage strength, remain unbroken when subjected to 503 newtons of force. *See, e.g.*, (PTX 2554); (PTX 2593); (PTX-2700); and (PTX-2661). It is true that two of the

¹³ Defendants note that upon visiting the Emerson Testing Facility during trial, the tablet pills were in far worse condition than when originally tested. *See* Trial Tr. at 1295–98. Moreover, the tablets had been covered in scotch tape. Trial Tr. at 1298:2–6. Defendants argue that Grünenthal, by covering the tablets with scotch tape after testing them, obscured the fact that they separated into multiple pieces after being tested. *Id.* at 1299:1–4. The court draws no such conclusions from Grünenthal's post-testing conduct. It is not surprising that the tablets, having been stored for a year, would be in a different condition than when initially tested. Moreover, Grünenthal's decision to cover the tablets with tape prior to storing them was reasonable given that testing was complete.

Actavis 30mg tablets tested showed significant deformation, and exhibited large fractures, in Dr. Davis's photographs. See PTX2569 at 0063. Similarly, a photograph of one of the tested Teva tablets, the 10mg tablet, shows a flake separated from the dosage form. See PTX 2667 at 0036. But these are the results of just three tests. Each dosage strength was in fact tested ten times. Thus, even though a photograph of one Teva's 10mg shows a flake, the other nine photographs of Teva's 10mg tablet show completely unbroken tablets. See PTX 2667 at 0036. The same is true of eight out of ten Actavis 30mg tablets, which show no hint of separating into two or more pieces. See PTX2569 at 0063. Given that each tablet was tested ten times, and that the overwhelming majority of tests indicated no hint of separating into two or more pieces, the court finds it probable that the Actavis 30mg tablets and Teva 10mg tablets have a breaking strength of more than 500N. The same is true regarding the other dosage strengths. Dr. Davis's photographs prove, by a preponderance of the evidence, that these tablets remain unbroken at pressures above 500N. Thus, the court concludes that defendants infringe the breaking strength limitation of the '060 Patent.

iv. Whether Defendants' Products Have a Separate Viscosity-Increasing Agent Which Forms a Gel With the Extract From the Dosage Form.

Claim 9 of the '060 Patent takes the dosage form described in Claim 1 and incorporates additional barriers to abuse beyond hardness, such as the use of an emetic, a nose/throat irritant, a dye, a "viscosity increasing agent," *et cetera*.

See '060 Patent at 21:37–52. Of these additional barriers to abuse, the only one that could possibly be found in defendants' products is the "viscosity-increasing agent," which when exposed to an aqueous liquid "forms a gel with the extract obtained." Trial Tr. at 149; '216 Patent at 21:41–46 (Claim 9 part (b)). The purpose of this additional barrier is to complicate abuse by injection. A drug abuser, upon attempting to dissolve a subverted tablet in a liquid, will discover that it forms a gel that is difficult to inject by needle. See Trial Tr. at 987.

As discussed in the claim construction section of this decision, the '060 Patent would be read by a person of ordinary skill in the art as requiring the viscosity-increasing agent to be distinct from the hardening polymer. See *supra* Part A(1)(c)(iv). Thus, Grünenthal must show that defendants' tablets, beyond having a hardening polymer, use some other substance, such as xanthan gum, to provide increased viscosity. It fails in this burden with regard to each of the four defendants. Neither Actavis, Impax, ThoRx, nor Teva¹⁴ have been shown to include a distinct viscosity-increasing agent, such as xanthan gum, in their generic products.

While defendants' products do not contain a separate viscosity-increasing agent, the court nonetheless concludes that defendants infringe part (b) of Claim 9 pursuant to the doctrine of equivalents. Each of defendants' tablets, as discussed, contain polyethylene oxide ("PEO"), At trial, Dr. Davis explained that

¹⁴ Defendant Teva did not dispute whether its product has a separate viscosity increasing agent. Trial Tr. at 1202:18–20. Nonetheless, it is Grünenthal's burden, as plaintiff, to show that Teva's drug infringes the asserted claims. Grünenthal has not shown that Teva's product contains a viscosity-increasing agent distinct from polyethylene oxide. See PX-5002.215; see also PTX 2657 at 5.

the PEO in defendants' tablets performs substantially the same function, in the same way, and achieves the same result as the xanthan gum in Endo's tablets. Trial Tr. at 1203.

The PEO in defendants' tablets makes it more difficult for abusers to prepare defendants' tablets for intravenous injection. This is because the PEO, aside from providing hardness, also functions to increase viscosity of the extract when exposed to water. See Trial Tr. at 1203-04. It does this in the same way as the xanthan gum in plaintiffs' products, by mixing with the aqueous liquid. Trial Tr. at 1204:2-6. It also achieves the same result as the xanthan gum in Endo's tablets. When defendants' tablets are milled and placed in a spoon containing water, the PEO forms a "slimy stick paste" that cannot be poured from the spoon. See Trial Tr. at 1204:19-21; *see also* Actavis Introduction to Overall Quality Summary (PTX-2367¹⁵ at 23622). Thus, the PEO in defendants' tablets, by performing the same function in the same way as a separate viscosity-increasing agent, and by achieving the same result, infringes part (b) of Claim 9 of the '060 Patent.

At trial, defendants argued that their products do not "form a gel" as required by the remainder of part (b) of Claim 9 of the '060 Patent. However, defendants' own submissions to the FDA, and Dr. Davis's testing of their tablets, show otherwise. As discussed, Actavis reported to the FDA that its milled tablets

¹⁵ Actavis objects to the admission of this exhibit, claiming it was "never discussed by any witness." That objection is overruled. Plaintiffs' expert, Dr. Davis, relied on the exhibit during his direct testimony. See Trial Tr. at 1169, and the court rules that it is relevant and not otherwise inadmissible. See Fed. R. Evid. 402

formed a “slimy sticky paste” when combined with water in a spoon. (PTX-2367 at 23622). In the court’s view, there is no significant difference between a “slimy sticky paste” and a “gel.” The court need not rely on semantics, however, to resolve whether defendants’ tablets “form a gel.” Dr. Davis, in testing defendants’ tablets, assessed each of them for whether they formed a gel when milled and placed in a vial of water. *See* Trial Tr. at 1359–60. The results of these tests, captured in photographs, speak for themselves. Each of defendants’ tablets form a thick and unmistakable gel when milled and placed in water. *See, e.g.*, PTX-2577 (showing the results of “gel testing” Actavis’s 7.5mg tablet).

Grünenthal has satisfied its burden and shown by a preponderance of the evidence that defendants’ tablets infringe Claim 9 of the ’060 Patent. Although their tablets do not contain a distinct viscosity-increasing agent as required by the claim, the PEO in their tablets satisfies the limitation under the doctrine of equivalents. Moreover, each of defendants’ tablets forms a gel as required by the claim.

v. Whether Defendants Infringe The Remaining Limitations of the Asserted Claims.

Having resolved the issues disputed at trial, the remainder of the infringement inquiry is straightforward. Grünenthal has proved by a preponderance of the evidence that defendants infringe the asserted composition and method claims of the ’060 Patent.

With regard to Claim 1, defendants’ tablets are, as discussed, “abuse-proofed thermoformed dosage forms.” Because defendants’ products contain the opioid oxymorphone, they indisputably have an “active ingredient with abuse

potential” as required by the claim. *See* '060 Patent at 21:6-7. Moreover, the hardening polymer used in defendants’ tablets, polyethylene oxide, satisfies part (C) of the claim. *Id.* at 21. Finally, as discussed above, defendants’ tablets satisfy the final limitation of the claim because they exhibit a breaking strength of at least 500N. Thus, defendants products infringe Claim 1 of the '060 Patent.

Because defendants’ tablets use polyethylene oxide as the hardening polymer, they infringe Claim 4 of the '060 Patent. *See* '060 Patent at 19:20–23 (“wherein the polymer is at least one polymer selected from the group consisting of polyethylene oxide”). Since the tablets are in a controlled release form, and because the PEO in them serves as the controlled release matrix material, defendants infringe on Claim 24 of the '060 Patent. Moreover, defendants’ tablets satisfy the limitations of claims 25 and 27 because they are made by mixing the components of Claim 1, press-forming that mixture, and then subsequently exposing it to heat. *See, e.g.*, Trial Tr. at 2548; *see also* '060 Patent at 23:1–12; DTX-2192 at 1236. Defendants induce infringement of the method recited in Claim 29 by instructing patients to administer the tablets to treat pain. *See, e.g.*, PTX-2352. Defendants’ tablets infringe Claim 30 because their hardening polymer, Polyox (the commercial version of polyethylene oxide) has a molecular weight above one million grams per mole. Trial Tr. at 1202:4–5. Defendants’ products satisfy claims 31 and 32 because they use oxymorphone as the active ingredient, and the dosage form is a tablet. They satisfy Claim 33 because the polyethylene oxide in their tablet comprises more than 60% of the dosage form by weight. *See, e.g.*, PTX-2589 at 10; PTX-2657 at 12. Likewise, each of the

defendants except for Teva, against whom it is not asserted, infringe Claim 34 of the '060 Patent because the content of their hardening polymer, polyethylene oxide, is at least 60% by weight relative to the dosage form.

The court concludes that plaintiffs have satisfied their burden and shown by a preponderance of the evidence that Actavis, Impax, ThoRx, and Teva infringe claims 1, 4, 9, 24, 25, 27, 29, 30, 31, 32, 33, and 34¹⁶ of the '060 Patent.

B. Whether the Patents-in-Suit are Invalid.

An invention is only patentable if it is novel. *See* 35 U.S.C. § 101. An invention is novel if there is no substantially identical matter disclosed by a piece of prior art. *See* 35 U.S.C. § 102(a). It goes without saying that an invention is not novel, and is therefore not patentable, if it simply recites a law of nature, natural phenomenon, or abstract idea. *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014). If an invention touches on natural phenomena, to be patentable it must provide additional elements such that the practice of the invention amounts to more than the practice of the natural phenomenon. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012). In addition to being novel, an invention must also be useful. *See* 35 U.S.C. § 101. An invention is “useful” if it confers substantial utility to society, meaning it provides some practical benefit to the public. *See Brenner v. Manson*, 383 U.S. 519, 534–35 (1966); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005).

Once awarded, a patent is presumed to be valid. 35 U.S.C. § 282(a). In an

¹⁶ Plaintiffs did not assert Claim 34 of the '060 Patent against Teva, so the court makes not findings or conclusion as to whether Teva infringes that claim.

action for patent infringement the defendant, regardless of whether it asserts non-infringement of the claims, may argue that the patent itself is invalid. 35 U.S.C. § 282(b). The defendant carries a heavy burden in this regard. It must prove the patent's invalidity by clear and convincing evidence, *Microsoft Cor. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242–43 (2011), meaning evidence that instills in the court an “abiding conviction” that the patent's invalidity is highly probable. *ActiveVideo Networks, Inc. v. Verizon Communications, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012).

Generally speaking, a defendant may prove the invalidity of a patent by showing that it is anticipated by a single prior art reference; or would have been obvious to a person of ordinary skill in the art at the time of the invention. See 35 U.S.C. §§ 102, 103. A patent will also be invalid if, more than a year before the patent application was filed, the invention was both ready for patenting and the subject of a commercial offer for sale, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67 (1998); or if the patent fails to provide a sufficient written description of the invention, fails to enable use of the invention, or is indefinite. See 35 U.S.C. § 112(a).

Anticipation requires that a single prior art reference disclose every element of the claimed invention. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). If the prior art reference fails to disclose a feature of the invention, it will only anticipate the invention if the “missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Id.*

To establish obviousness, a defendant “must demonstrate by clear and

convincing evidence that a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706–07 (Fed. Cir. 2012). In determining whether a patent claim is obvious, the court will consider “the scope and content of the prior art; the level of ordinary skill in the art; the differences between the claimed invention and the prior art; and evidence of secondary factors, also known as objective indicia of nonobviousness.” *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)) (internal numbering omitted). Objective indicia of non-obviousness include the commercial success of the invention, the invention’s satisfaction of a long-felt but unmet need, the failure of others to solve the problem at hand, and the copying of the invention by others. *Graham*, 383 U.S. at 17.

As mentioned, a patent will be invalid if the invention was both “ready for patenting” and the subject of a commercial offer for sale more than one year before the patent application was filed. See 35 U.S.C. § 102(b); *Pfaff*, 525 U.S. at 67. This is known as the “on-sale bar.” An invention is “ready for patenting” if it has been reduced to practice, meaning actually made, or if it has been sufficiently described or depicted in drawings by the inventor to enable a person skilled in the art to make the invention. See *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1373 (Fed. Cir. 2008). A commercial offer for sale occurs where the invention is marketed commercially. *Pfaff*, 525 U.S. at 67. This includes both

actual sales of the invention and offers to sell the invention. *Hamilton Beach Brands, Inc. v. Sunbeam Products, Inc.*, 726 F.3d 1370, 1374 (Fed. Cir. 2013). However, a commercial sale does not occur where the transaction is for experimental purposes. *Pfaff*, 525 U.S. at 67. The transaction will be for experimental purposes if represents a “bona fide effort to bring the invention to perfection, or to ascertain whether it will answer the purpose intended,” rather than represent an effort to earn profits. *Honeywell Int’l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 998 (Fed. Cir. 2007) (quoting *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 136 (1877)).

A patent must also meet the requirements of 35 U.S.C. § 112, which requires the specification to contain a sufficient description of the invention, to enable make and use of the invention, and to be sufficiently definite. See 35 U.S.C. § 112(a)–(b). A specification has a sufficient written description if it “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date” of the patent application. *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1351 (Fed. Cir. 2011). The enablement requirement is satisfied if the specification allows a person of ordinary skill in the art to make and use the invention without undue experimentation. 35 U.S.C. § 112 (a); *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). Finally, “a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig Instruments, Inc.*,

134 S. Ct. 2120, 2124 (2014).

1. Whether the Asserted Claims of the '122 and '216 Patents are Invalid.

Defendants argue that the asserted claims of the '122 and '216 patents are invalid for three reasons. First, they argue that the patents are invalid as obvious in light of the prior art at the time of the invention, October 15, 2001. Second, they argue that the '122 and '216 patents are invalid under the on-sale bar because they were ready for patenting and the subject of a commercial offer for sale more than a year before the patent applications were filed. Third, they argue that the patents fail to satisfy the written description, enablement, and definiteness requirements of 35 U.S.C. § 112.

a. Whether Endo's Invention Would Have Been Obvious to a Person of Ordinary Skill in the Art.

Defendants argue that Endo's invention, embodied in the asserted claims of the '122 and '216 patents, would have been obvious to a person of ordinary skill in the art at the time the patent applications were filed. There was general consensus at trial regarding the definition of a person of ordinary skill in the art in 2001. The parties agreed that such a person would have "at least a master's degree or a doctorate in pharmaceutical sciences with experience in developing formulations, including controlled release formulations. If the individual had a lesser degree of training, such as a bachelor's degree, then he would need several more years of experience in the areas of pharmaceutical formulation development." Trial Tr. at 1502:13–20.

This is where the parties' consensus ended. In all, the parties highlight

four areas in dispute regarding the obviousness/non-obviousness of Endo's invention¹⁷: (i) whether there was a motivation to select oxymorphone for use in a controlled-release delivery system; (ii) whether the prior art discloses the dissolution ranges claimed in the '122 and '216 patents; (iii) whether the pharmacokinetic limitations of the patent claims are obvious or otherwise invalid; and (iv) whether secondary factors indicate the invention's non-obviousness.

i. Whether There Was a Motivation to Select Oxymorphone For Use in a Controlled Release Setting.

The first area of dispute with regard to obviousness of the '122 and '216 patents is whether an ordinarily skilled artisan would be motivated to select oxymorphone for use in a controlled release setting.

Oxymorphone was known at the time of the invention. At trial, Dr. Banakar explained that opioids, as a family of molecules, have long been known in the art for their analgesic effect. *See* Trial Tr. at 1460. Oxymorphone specifically was known, and in fact had been approved and marketed under the branded name Numorphan between 1959 and 1971. Trial Tr. at 2623:17–21. Numorphan would be known to a person of ordinary skill in the art in 2001 because it had been included in the Physician's Desk Reference as early as 1969. *See* Physician's Desk Reference, Twenty-Third Edition (1969) at 698 (DTX-2890) (describing "Numorphan (oxymorphone) hydrochloride [as] a semisynthetic

¹⁷ Endo stipulated to the disclosure in the art of hydrophilic and hydrophobic materials, gelling agents, matrix formation, and other disclosures. *See* Stipulation and Order at 2–3, No. 12-CV-8060 (Mar. 27, 2015) (Dkt. #152).

narcotic . . . indicated for all instances of pain . . . [administered] Orally . . . every 4 to 6 hours.”). But while Numorphan was known in the art, it was also understood to be an immediate-release drug, to be taken every four to six hours. Trial Tr. at 1458:13–15. Endo had also been selling oxymorphone in intravenous and suppository forms, both of which are immediate release formulations. See Trial Tr. at 247–48, 450:7–9.

Although oxymorphone was known for use in immediate release form, it had never been integrated into a controlled release setting. This is not surprising given the state of the art in 2001.

Controlled release platforms were themselves known to persons of ordinary skill in the art at the time. Trial Tr. at 1474–75. For example, a patent awarded in 1997, Number 5,662,933 (the “Baichwal Reference”) taught the use of the TIMERx system, the same system Endo licensed from Penwest, with a “wide variety” of active ingredients, including the analgesics aspirin, codeine, morphine, dihydromorphone, and oxycodone. See Baichwal Reference at 8:29–30 (DTX-3559). Moreover, the 1999 Physician’s Desk Reference listed two controlled release opioid tablets, MS Contin and OxyContin, both of which used hydrophilic delivery systems. See Physician’s Desk Reference at 2556, 2569–79, Fifty-Third Edition (1999) (DTX 2870 and DTX 2961); *see also* Trial Tr. at 1476. However, while these pieces of art taught the integration of some opioids in a controlled release setting, they were silent in regard to integrating *oxymorphone* into a controlled release setting.

The teaching of the prior art indicates that selecting oxymorphone for use

in a controlled release setting would have been counterintuitive because of its exceptionally low bioavailability. As plaintiffs' expert Dr. Salomon Stavchansky testified, bioavailability refers to the amount of drug that survives metabolism in the liver and gut and enters the bloodstream, where it will be available to provide a therapeutic effect. See Trial Tr. at 2608–09. The 2000 Physician's Desk Reference reported the bioavailability of oxycodone at 60–87% and morphine at 40%. See Physician' Desk Reference at 2527, 2537, 54th Edition (2000) (PTX-404 and PTX-0532). Hydromorphone had a bioavailability of between 20% and 60% depending on the source. Compare Sarhill *et al.*, *Hydromorphone: pharmacology and clinical applications in cancer patients* at 86 (2000) (DX-3157) with Ritschel and Kearns, *Handbook of Basic Pharmacokinetics* at 491 (5th ed. 1998) (PTX-509). Oxymorphone had a reported bioavailability of just 10%. See Gordon *et al.*, Opioid Equianalgesic Calculations, 2 J. Palliative Med at 212 (1999) (PTX-117).

The art available in 2001 taught that bioavailability is a significant, even crucial, factor in evaluating a drug's suitability for placement in a controlled release vehicle. See U.S. Patent Number 5,958,452 (the "Oshlack Reference") at 2:47–50 (DTX-3560) ("[D]issolution time and . . . bioavailability . . . are two of the most significant fundamental characteristics for consideration when evaluating sustained-release compositions."). This is because bioavailability was suspected to influence a drug's inter-subject variability, meaning the differences in its clinical effect among a group of patients. See Hellriegel *et al.*, *Interpatient variability is related to the extent of absorption*, 60 Clinical Pharmac. & Therap.

at 604 (1996) (PTX-461) (“Our results clearly show a significant relationship between the absolute bioavailability of an oral dosage form and its intersubject . . . variation”). The lower a drug’s bioavailability, the more likely the drug will be to produce variations in clinical effect among a group of patients. *Id.*; see also Trial Tr. at 26:20–24. This effect on intersubject variability was suspected to be more pronounced given other influences, including a patient’s food consumption and amount of restedness. See William H. Barr, *Bioavailability of Oral Solid Dosage Forms and Clinical Response to Drug Therapy* at 58-59 (1973) (PTX-412).

As a result of its exceptionally low bioavailability, oxymorphone was considered by those skilled in the art to be a poor candidate for controlled-release treatment. Indeed, in an article in the Journal of Pharmaceutical Sciences, a group of authors explained that oxymorphone is ideally suited for delivery through the skin since it “is not very effective orally.” See Aungst *et al.*, *Transdermal Oxymorphone Formulation Development and Methods for Evaluating Flux and Lag Times for Two Skin Permeation-Enhancing Vehicles*, 79 J. Pharmac. Sciences at 1072 (PTX-410). Moreover, the art taught that because drugs like oxymorphone are almost wholly metabolized upon first passing through the liver, the only way to increase the amount of drug that survives to the bloodstream is to use an exceptionally large dose from the beginning, potentially “risking toxicity.” Read *et al.*, *Gastrointestinal Dynamics and Pharmacology for the Optimum Design of Controlled-Release Oral Dosage Forms*, 4 CRC Critical Reviews in Therap. Drug Carrier Systems 221, 240 (PTX-505).

Controlled release delivery systems were suspected of actually reducing

certain drugs' bioavailability due to a phenomenon known as "saturable first pass metabolism." Trial Tr. at 2640. Some drugs, when administered in immediate release form, "saturate" or exhaust the liver's metabolizing enzymes, allowing the remainder of the drug to enter the bloodstream unopposed. See Welling & Dobrinska, *Dosing Considerations and Bioavailability Assessment of Controlled Drug Delivery Systems* at 258 (1986) (PTX-526). Controlled release drugs, because they release the active ingredient slowly, may never "saturate" the liver's defensive enzymes, and will thus be blocked far more efficiently than their immediate release counterpart. *Id.*; see also Mordenti and Williams, *Controlled Release Drug Delivery: Pharmacodynamic Consequences* at 208–09 (1988) (PTX-491) ("controlled release formulations have less of a tendency to produce saturable first pass metabolism"). To a person of ordinary skill in the art, the saturable first pass phenomenon would have, at least to some degree, cautioned against selecting oxymorphone, a low-bioavailability opioid, for controlled-release treatment.

The notion that low-bioavailability drugs were considered unsuitable for extended-release formulation is reinforced by the fact that, until Endo's development of OPANA®ER, there were remarkably few such examples. At trial, Endo and its experts repeatedly emphasized that at the time of its invention, OPANA®ER was the lowest-bioavailability drug, by a wide margin, ever formulated into a controlled-release setting. See, e.g., Trial Tr. at 2655-56, see also Plaintiff's Opening Statement Slide Deck at 001.92 ("Why Oxymorphone? . . . Lower bioavailability than any prior controlled release formulation."). During

cross-examination of Endo's expert Dr. Stavchansky, defendants revealed that another low-bioavailability drug, oxybutynin (bioavailability of 6%), had previously been developed into a controlled release formulation. *See* Trial Tr. 2779. But in the court's view, this merely served to underscore, rather than diminish, the fact that low bioavailability drugs were remarkably rare in controlled-release settings. Dr. Stavchansky's unmistakable surprise upon being confronted with Oxybutynin's low bioavailability, and its total absence from the expert reports of both sides, impressed on the court that low-bioavailability drugs were, at the time of the invention, perceived as unsuited for development into controlled release forms.

Defendants argue that, rather than teach away from the selection of oxymorphone, the prior art actually discloses its use in the type of controlled-release setting embodied in the '122 and '216 patents. The first of these pieces of prior art is an application for an international patent application filed in 2000. *See* PCT International Publication No. WO 01-09661 A2 (the "Maloney Reference") (DTX-3561). The second piece of prior art is United States Patent Number 5,958,452 (the "Oshlack Reference") (DTX-3560).

The Maloney Reference describes a sustained-release formulation for opioid compounds that avoids the need for certain product features hitherto common in sustained release formulations. *See* Maloney Reference at 8. In describing this invention, Maloney clearly discloses the type of controlled-release matrix delivery systems asserted in Claim 1 of the '122 Patent and claims '72 and '77 of the '216 Patent. *See* Maloney Reference at 6–7, 9. However, the

Maloney reference claims as its invention “an improved formulation for the sustained release of *oxycodone*,” not oxymorphone. *Id.* at 7 (emphasis added). Indeed, each of the many examples provided in the Maloney Reference deal exclusively with oxycodone hydrochloride, *id.* at 15–17, a completely different opiate from that embodied in the ’122 and ’216 patents.

The Maloney Reference does mention the use of oxymorphone. However, it does so by sheer overinclusion, by simply listing dozens of molecules and purporting to cover them as part of the invention. First, Maloney discloses controlled release dosage forms combined with an “opioid compound.” *Id.* at 8. This opioid compound is defined to preferably include *all* opioid analgesics, meaning the “diverse group of drugs . . . that displays opium or morphine-like properties.” *Id.* at 9. Maloney then goes further, providing a list of 65 molecules considered to be opioid analgesics. *Id.*; *see also* Trial Tr. at 1671. This list includes oxymorphone. Maloney at 9. It also includes heroin, opium, and fentanyl. *Id.*

The court finds it difficult to believe that a person of ordinary skill in the art, upon reading Maloney, would understand oxymorphone to be suitable for a controlled release setting. Maloney’s vast listing of molecules, inclusion of heroin, opium, and fentanyl, raises doubts as to whether that list would be taken seriously as indicating suitability for controlled release treatment. *See* Trial Tr. at 1671; *see also* Maloney at 8–9 (“Preferably the opioid compound included in the formulation is an opioid analgesic Opioid analgesics include . . . heroin . . . opium . . . etc . . .”). Indeed, fentanyl was widely understood as only suitable

for transdermal, not oral, delivery. Trial Tr. at 1672. In all, Maloney mentions oxymorphone four times. See Maloney Reference at 9, 13, 26, 28. However, in each instance where oxymorphone is mentioned, it is situated among dozens of molecules, such as fentanyl, whose suitability for inclusion in a controlled-release setting is not established in the reference. *Id.*

Maloney is also silent as to the dosing interval of the invention. A primary feature of Endo's invention, embodied in the first claims of both the '122 and '216 patents, is that Endo's tablet will be suitable for a 12 hour dosing interval, meaning the patient will only have to take the tablet twice per day. See '122 Patent at 25:50–53; '216 Patent at 26:52–53. Maloney does provide dissolution data for oxycodone hydrochloride, but for reasons that will be discussed below, this data was measured using methods that would not give any indication of the *in vitro* dissolution rate of oxymorphone, which Endo was the first to measure and which it claimed in its patents. See Maloney Reference at 21. A person of ordinary skill in the art, upon reading Maloney, would have no understanding of the dosing interval of controlled-release oxymorphone.

The Oshlack Reference shares the Maloney Reference's deficiencies, and adds its own. The Oshlack reference describes using "melt extrusion technology" to produce sustained-release dosage forms, where such technology had previously been used only for immediate release formulation. Oshlack Reference at 1:10–15. Like Maloney, Oshlack discloses the use of "sustained-release matrix pharmaceutical formulations." *Id.* However, it only discloses the use of hydrophobic delivery systems, not hydrophilic systems. Oshlack Reference at

3:39–49; 6:44. In describing suitable active ingredients, Oshlack includes opioid analgesics, but like Maloney, simply lists 72 molecules as covered without regard as to whether they would actually be suitable for use in a controlled release setting. *Id.* at 8-39. Indeed, Oshlack includes heroin, opium, and fentanyl as suitable opioid analgesics. *Id.* But just as with Maloney, it is doubtful that these active ingredients would be understood as capable of being housed in a controlled release delivery system. *See also* Trial Tr. at 1671–72 (“There is no controlled release oral formulation of fentanyl available, but there is a controlled release dermal formulation which is applied on the skin.”).

While Oshlack contains examples providing dissolution data for certain active ingredients, it only does so for chlorpheniramine, morphine, oxycodone, hydromorphone, dilaudid, tramadol, and stearyl alcohol. Oshlack Reference at 14–25. It does not list a single example using oxymorphone. This is notable because, as discussed, oxymorphone has a much lower bioavailability than any of the opioids listed as examples. Beside listing oxymorphone among other potential active ingredients, *see, e.g.*, Oshlack at 7:37–38, Oshlack simply gives no indication, to a person of ordinary skill in the art, that the opioid could actually be integrated into a controlled release setting, much less a setting providing a 12 hour dosing interval.

The court is persuaded by the expert testimony that the art taught away from the selection of oxymorphone for use in a controlled release setting because of its exceptionally low bioavailability. Defendants failed to show that a person of ordinary skill in the art would, upon reading the Maloney, Oshlack, and other

prior art references, be motivated to select oxymorphone for development into a controlled release formulation.

ii. Whether the Prior Art Discloses the Claimed Dissolution Rates.

As discussed above, the prior art in 2001 taught away from the selection of oxymorphone for use in a controlled release setting. But even if an artisan were motivated to select oxymorphone, a key feature of Endo's invention is the pairing of oxymorphone with a controlled-release delivery system which releases the active ingredient at a specified rate. *See, e.g.*, '122 Patent 25:55–60. Three of the four claims asserted from the '122 Patent contain dissolution limitations. *See* claims 2, 3, and 19; '122 Patent at 25–28. Likewise, nineteen of the twenty asserted claims from the '216 Patent recite (directly or by reference) dissolution limitations. *See* claims 22, 40 and 42,¹⁸ 50, 54, 57, 62, 64, 71, 73, 74, 78, 79, 80, 82. '216 Patent at 26–34. Thus, crucial to defendants' assertion of obviousness is whether the prior art discloses to a person of ordinary skill the dissolution ranges recited in the '122 and '216 patents.

This creates two problems for defendants' obviousness argument. First, each of the prior art references relied on by defendants discloses the dissolution profile of a drug with an active ingredient other than oxymorphone. *See* Oshlack Reference at 18–19 (oxycodone); Baichwal Reference at 15:32–40 (albuterol); Maloney Reference at 23 (oxycodone). Second, most of the prior art references defendants relied on used different methods to test dissolution than that used

¹⁸ Although mentioned here, the court makes no conclusions regarding the validity of claims 40 and 42 of the '216 Patent because defendants do not infringe those two claims.

in the '122 and '216 patents. *Compare* Maloney Reference at 23 (using the USP Basket Method at 100 revolutions per minute) *with* '122 Patent at 26:65–68 (using the USP Paddle Method at 50 revolutions per minute).

To demonstrate the obviousness of Endo's dissolution claims, it was incumbent on defendants to show two things at trial: (1) that a person of ordinary skill, upon reading the prior art, would understand oxymorphone to be interchangeable with other active ingredients in a controlled release delivery system; and (2) that the results of the dissolution testing methods used in the prior art could be read to indicate the results of the dissolution testing methods used in the Endo patents.

1. A Person of Ordinary Skill in the Art Would Not Understand Oxymorphone to Be Interchangeable With Other Active Ingredients in the TIMERx System.

At trial, Dr. Banakar testified that the TIMERx system Endo licensed from Penwest was essentially “plug and play,” meaning that one could take Penwest's controlled-release delivery system and easily insert various suitable active ingredients. Trial Tr. at 1516:21–22. (“Now they plug and play, they changed the drug and put another drug and provide the system that I am looking for.”). Referring to Penwest's 1997 filing with the Securities and Exchange Commission, Dr. Banakar noted that various drug substances had been paired with TIMERx, including the heart drug Nifedipine and, pursuant to Endo's development work, oxymorphone. Trial Tr. at 1519:7–25. In Dr. Banakar's opinion, different active ingredients may be readily interchanged in the TIMERx system. Trial Tr. at 1522–23 (“Baichwal discloses . . . the TIMERx platform using gums. Baichwal also

discloses analgesics which could be put into these gums to get controlled release formulations for morphine A person of ordinary skill in the art would be able to develop a controlled release formulation for oxymorphone using the same technology as Baichwal discussed.”). Thus, in his view a person of ordinary skill in the art, upon learning that other molecules had been paired with TIMERx, would find it obvious to do the same with oxymorphone.

Plaintiffs’ expert on non-obviousness, Dr. Stavchansky, disagreed with Dr. Banakar’s characterization of the TIMERx technology as a “plug and play” system. *See* Trial. Tr. at 2680:4–5. Dr. Stavchansky noted that different opioid molecules have different pharmacokinetic effects, and the fact that one opioid has been integrated into a controlled release setting does not indicate similar success for a different opioid. *Id.* at 2681. It is only upon testing the new opioid in the controlled-release setting under both laboratory conditions and in live subjects that one can assess its compatibility with the TIMERx system. *See id.* To support this opinion, Dr. Stavchansky compared two controlled release drugs marketed by Purdue Pharma, MS Contin (morphine) and OxyContin (oxycodone), and discovered that even though both use the same controlled-release technology, they exhibit significantly different formulations. Trial Tr. at 2686–88. This indicates that it is no simple matter to “plug” a new active ingredient into a previously used delivery system.

The court finds Dr. Stavchansky to be more persuasive than Dr. Banakar on this issue. The court is not persuaded that controlled release systems, including TIMERx, would be understood by artisans as simply “plug and play.”

This is because, as Dr. Stavchansky testified, each controlled release drug is independently formulated and tested. A person of ordinary skill in the art, upon learning that one opioid had been developed into a controlled release formulation, would not find it obvious to do the same with oxymorphone.

2. Dissolution Profiles Measured Using the USP Basket Method and Paddle Method at 100rpm Were Not Known to Teach Dissolution Profiles Measured Using the USP Paddle Method at 50rpm.

Even if the court were to accept defendants' argument regarding the interchangeability of oxymorphone and other active ingredients in controlled release systems such as TIMERx, the prior art would still fail to teach Endo's claimed dissolution ranges. Since OPANA®ER was the first drug to integrate oxymorphone into a controlled release setting, all of the prior art references disclose the dissolution rates of *other* controlled release drugs such as albuterol and oxycodone. *See, e.g.*, Baichwal Reference at 14:36-41 (showing dissolution for albuterol, a non-opioid). The person of ordinary skill in the art would have to assume that the disclosed dissolution rate of drugs such as albuterol and oxycodone would somehow be indicative of the dissolution rate Endo claimed for controlled-release oxymorphone.

But even if the artisan were to make this assumption, which the court is not convinced is reasonable, he would have to appreciate some way to correlate the dissolution profiles of the non-oxymorphone controlled release drug to the dissolution profile of controlled-release oxymorphone. This presents a significant challenge to defendants' obviousness argument, because most of the prior art

references measured dissolution using different testing methods than what Endo used in its dissolution claims.

The Endo patents express the dissolution profile for controlled-release oxymorphone using the USP Paddle Method at 50rpm. See '122 Patent at 25:57. Where, for example, the Endo patents say that a tablet releases 45% to 80% of the active ingredient within four hours, they mean four hours after being placed in a vessel containing 500ml of medium that is agitated by the spinning of paddle-shaped blades at fifty revolutions per minute. See *supra* Part A(1)(a).

Most of the prior art references defendants rely on measured dissolution in a different way. The Maloney Reference measured dissolution of controlled-release oxycodone using the USP Basket Method at 100rpm. See Maloney Reference at 23. The same is true of another reference, United States Patent Number 5,549,912 (the "912 Patent"). See '912 Patent at 2:20–25 (DTX-0042). The Oshlack Reference measured dissolution using the Paddle Method, but did so at twice the speed as Endo, 100 revolutions per minute, and in nearly twice the aqueous buffer (900ml compared to Endo's 500ml of media). See Oshlack Reference at 11:66.

While Maloney and Oshlack measured dissolution differently than Endo, some of their dissolution ranges coincide with those claimed for oxymorphone in the '122 and '216 patents. For example, the Maloney Reference shows that certain oxycodone hydrochloride tablets will be 25% dissolved at one hour. *Id.* The Oshlack Reference shows dissolution of 12.5% to 42.5% at one hour. See Oshlack Reference at 12:24–27. Both are similar to the dissolution range Endo

claimed for oxymorphone, 15% to 50% at one hour. See '122 Patent at 25:57–60.

But to accept that Oshlack, Maloney, and the '912 Patent taught the dissolution ranges claimed in the '122 and '216 patents, the court would have to accept that a person of ordinary skill in the art would understand some correlation between results obtained using the Paddle and Basket methods at different speeds.

Dr. Banakar suggested that two pieces of art, the Hanson Reference and the Madden Reference, taught such a relationship between the two methods. Trial Tr. at 1551–52. The “Hanson Reference” is a handbook on dissolution testing published in 1991. See William A. Hanson, *Handbook of Dissolution Testing* (2d Ed. 1991) (DTX-3556). It provides that “for general purposes when not otherwise specified—rates of 50 rpm for the paddle and 100 rpm for the basket are recommended and have proved to be *roughly equivalent* to one another in producing dissolution.” *Id.* at 36 (emphasis added). Similarly, in a 1998 report presented to the American Association of Pharmaceutical Scientists, a group of authors observed that the four USP dissolution testing methods, including the Paddle and Basket Methods, produce similar dissolution profiles “regardless of the degree of agitation” See Madden *et al.*, *Impact of Apparatus Type and Hydrodynamics on the Release of a Highly Soluble Drug From a Hydrophilic Matrix Tablet* (the “Madden Reference”) (DTX-0069 at 9956).

However, a significant body of other art showed no such relationship. A textbook published in 1999 stated that:

“the use of various testing methods makes it even more difficult to

interpret dissolution results because there is no simple correlation among dissolution results obtained with various methods. For many drug products, the dissolution rates are higher with the paddle method No simple correlation can be made for dissolution results obtained with different methods.”

Shargel and Yu, *Applied Biopharmaceutics & Pharmacokinetics* at 145 (1999) (PTX 637) (the “Shargel Reference”). Similarly, a book written by defendants’ own expert, Dr. Banakar, stated that the dissolution testing device used is one of six factors influencing dissolution rate. See Umesh Banakar, *Pharmaceutical Dissolution Testing* at 133–34 (PTX-411) (the “Banakar Reference”). Finally, an article published in 1978, the Hardwidge Reference, taught that different dissolution testing methods produce different results depending on the speed of agitation. See E.A. Hardwidge *et al.*, *Comparison of Operation Characteristics of Different Dissolution Testing Systems*, 67 J. Pharmaceutical Sciences 1732 (1978) (PTX-0458) (the “Hardwidge Reference”). Hardwidge shows that the Paddle Method at 100rpms produces significantly faster dissolution over time than the Paddle Method at 50rpm. See Hardwidge Reference Fig. 1. Moreover, when dissolution is tested for the Paddle and Basket Methods at the same speed of agitation, the Paddle Method will produce faster dissolution results. Compare *id.* Fig. 1 with *id.* Fig. 2.

Even accepting, without approving, defendants’ argument that a person of ordinary skill in the art would understand the dissolution profiles for the controlled release formulation of one molecule as teaching the dissolution profile

for the controlled release formulation of a wholly different molecule,¹⁹ the court remains unpersuaded that the art in 2001 taught the interchangeability of the USP Paddle Method and USP Basket Method at different speeds. At most the Hanson Reference merely provided that the two methods were “roughly equivalent in producing dissolution.” This would be woefully insufficient instruction to a person of ordinary skill in the art, and would provide no way to infer some correlation between dissolution results obtained using the different methods. Rather than teach the equivalency of the various USP testing methods, a significant body prior art, including the Shargel, Banakar, and Hardwidge references, taught that dissolution results from one testing method were non-interchangeable with results obtained from a different testing method.

The court concludes that defendants have failed to show disclosure in the art of the dissolution limitations claimed in the '122 and '216 patents. The court is unpersuaded that a person of ordinary skill in the art would understand oxymorphone to be interchangeable with oxycodone, morphine, and albuterol in a controlled release setting, nor is it clear that he would understand dissolution values for those drugs as indicating the dissolution profile of controlled-release

¹⁹ The court is willing to accept this assumption only to a certain point. Two prior art references use the Paddle Method at 50rpm but nonetheless fail to disclose the claimed ranges for other reasons. The Baichwal Reference shows the dissolution profile of albuterol, which isn't an opioid. See Baichwal Reference at 14:36-41 (using the Paddle Method at 50rpm). The court is unwilling, given the defendants' high burden, to go so far as to accept that the dissolution of a non-opioid would indicate to an artisan the dissolution of oxymorphone. A 1999 article shows the dissolution profile of an opioid, morphine sulfate, measured using the Paddle Method at 50rpm. See Webster *et al.*, *In Vitro Studies on the Release of Morphine Sulfate From Compounded Slow-Release Morphine-Sulfate Capsules* at 3, *Int'l J. Pharmaceutical Compounding* (1999) (the “Webster Reference”) (DTX-0028). But while morphine is an opioid, the article provides dissolution values falling outside of those later claimed by Endo for oxymorphone. Compare Webster Reference at Fig. 2 (showing dissolution of morphine sulfate of ~80% at four hours) with '216 Patent at 34:36-40 (showing dissolution of oxymorphone of 58-66% at four hours).

oxymorphone. Even if a person of ordinary skill in the art made this assumption, the dissolution data provided in prior art would not predict or indicate Endo's claimed ranges because it was obtained using different testing methods. Because there was no way to equate the results obtained from the different testing methods, a person of ordinary skill in the art would not have been able to extrapolate from the prior art the dissolution limitations claimed in the '122 and '216 patents.

iii. Whether the Claimed Pharmacokinetic Limitations are Obvious or Otherwise Invalid.

In addition to the dissolution limitations discussed above, the '122 and '216 patents also recite pharmacokinetic limitations, or limitations describing how Endo's tablets will affect the human body once ingested. The pharmacokinetic limitations of the patents can be grouped into four broad categories: "analgesic effect" limitations (providing that the tablet will provide pain relief for a certain period of time); "food effect" limitations (limitations describing blood concentration levels after having eaten a meal as opposed to having fasted); metabolite limitations (limitations stating that ingesting the tablets will produce the metabolite 6-OH oxymorphone); and peak plasma level limitations (limitations describing when and how often patients' blood will exhibit peak concentrations of oxymorphone). *See, e.g.*, '216 Patent at 26:35–55; *see also supra* parts (A)(1)(a)–(b).

Defendants challenged the validity of the asserted pharmacokinetic limitations at trial, arguing that: (1) some of the asserted pharmacokinetic limitations are the result of natural phenomena and therefore not patentable; (2)

even if those pharmacokinetic limitations are patentable, they were nonetheless obvious in light of the prior art; and (3) the claimed pharmacokinetic limitations could have been predicted by a convolution analysis. The court will address each of these arguments in turn.

1. The Claimed Pharmacokinetic Limitations Do Not Merely Recite Natural Phenomena.

Defendants argue that some of the pharmacokinetic limitations claimed in the '122 and '216 patents merely capture natural phenomena and are therefore ineligible for patent protection. *See* Trial Tr. at 177:6.

Many of the asserted claims capture what are known as “food effects,” meaning they provide that concentrations of oxymorphone or its metabolite in the bloodstream will vary to a certain extent depending on whether a patient has eaten or fasted. For example, claims 20 of the '122 Patent and 40 of the '216 Patent provide that total blood concentrations of oxymorphone ($AUC_{(0-in\infty)}$) will be no more than 20% higher when the tablet is taken after having eaten a meal as opposed to having fasted; and that maximum observed concentrations of oxymorphone (C_{max}) will be no more than 50% higher after having eaten. *See* '122 Patent at 26:54–58; '216 Patent at 30:10–12 (depending from Claim 38).

Other limitations of the patents describe “peaks,” or highpoints, of oxymorphone concentration in the blood occurring within one to eight hours, and then recurring once or twice more within twelve hours. *See, e.g.*, '216 Patent at 26:35–55. Finally, some of the claims provide that the formulation will provide detectable levels of oxymorphone and its metabolite 6-OH oxymorphone, and in

certain ratios. *See id.*

At trial, Dr. Banakar testified that the food effect, peak concentration, and “detectable level” limitations of the ’122 and ’216 patents are the result of the body’s natural processes, and would be exhibited whenever oxymorphone is administered to human subjects. *See, e.g.*, Trial Tr. at 1571:17–24. With regard to the food effect limitations, Dr. Banakar testified that Endo merely administered controlled-release oxymorphone to subjects and then claimed the resulting blood concentrations. Trial Tr. at 1572:7–11. For example, Dr. Banakar claimed that Endo performed a food effect study in subjects which showed total blood concentration (AUC) of oxymorphone to be 18% higher after having eaten a meal as compared to having fasted, and simply recited as a claim limitation AUC values of not greater than 20%. Trial Tr. at 1572. Endo purportedly used a similar strategy in reciting the claim limitations for maximum observed concentrations of oxymorphone (C_{\max}). *Id.*

At trial, defendants’ expert failed to cite any reference for the proposition that the food effect limitations merely capture natural phenomena, other than opining to that effect. *See* Trial Tr. at 1501:21-25, 1571:13-16. Dr. Banakar offered no other support for his view that the pharmacokinetic limitations are the result of the body’s natural processes. Of course, the court gives considerable weight to Dr. Banakar’s opinion given his clear expertise in the field. But the court finds his testimony to be undermined by the fact that oxymorphone, when administered in an immediate release formulation, produces a total blood concentration (AUC) of 30% under fed conditions. Trial Tr. at 484:6–9; ’122

Patent at 10:18–20. This is considerably higher than the food effect of controlled release oxymorphone, which when taken under fed conditions produces total blood concentration (AUC) of 20%. Trial Tr. at 486:9–14. If the food effect of oxymorphone was merely a result of natural processes, then one would expect the same total blood concentration (AUC) after eating for both the immediate release and controlled release formulations. This is not the case. Rather, it appears that formulating oxymorphone into a controlled-release setting curbs the pronounced food effects exhibited by immediate release oxymorphone, reducing them to more tolerable levels. *Cf.* Trial Tr. at 487–88. It is the inventive dosage form, and not merely the body’s metabolism, that provides the significant reduction in food effects claimed in the Endo patents.

The invention has an equally significant effect on the number of peaks in oxymorphone blood concentration levels. When immediate release oxymorphone is ingested, the subject’s blood exhibits a single dramatic peak in blood concentration levels occurring in the first four hours, and a second, much smaller peak occurring at about twelve hours. *See* ’122 Patent at Fig. 5. When controlled-release oxymorphone is ingested, the subject’s blood exhibits three moderate peaks in blood concentration levels over about twelve hours. *Id.* The highest peak occurs within eight hours. *Id.* Endo claimed these multiple-peak and highest-peak effects as limitations in the ’216 Patent. *See, e.g.,* ’216 Patent cls. 1, 78.

At trial, Dr. Banakar opined that the “multiple” peaks exhibited by controlled release oxymorphone were the result of a natural process known as

“enterohepatic recirculation.” Enterohepatic recirculation means that once ingested, oxymorphone is circulated between the intestine, liver, and bile duct multiple times, resulting in multiple peaks in blood concentration levels. See Trial Tr. at 1495. Indeed, in correspondence Endo submitted to the FDA in 2002, Endo explained that “the presence of multiple peaks . . . suggests the presence of enterohepatic recycling” Study of Human Pharmacokinetics and Bioavailability Data (Nov. 14, 2002) (DTX-1444 at 4173). Thus, it is Dr. Banakar’s opinion that the multiple-peak limitations of the asserted claims merely describe the natural phenomena of enterohepatic recirculation of oxymorphone.

Dr. Banakar’s observation appears sound, but the conclusion he draws is not. The “multiple peaks” that occur following administration of controlled release oxymorphone are of course the result of the body’s natural processes. It could be no other way. But Endo’s patents do not pretend to claim the natural process of enterohepatic recirculation. Rather, the Endo patents claim a dosage form for oxymorphone that provides an analgesic effect over twelve hours, *see* ’122 Patent at 25:50–52, and which causes multiple peaks in blood concentration levels (and ensuing continued analgesic effectiveness) during that same period. ’216 Patent at 34:20–24. Similarly, Endo claimed that that blood levels will peak within 8 hours of administration, *id.* cl. 1, as opposed to within 4 hours as would be expected with immediate release oxymorphone.

These pharmacokinetic effects *are only possible* because the dosage form, the invention itself, slows the release of oxymorphone to such a degree that: (1)

peak blood concentration of oxymorphone occurs later (within 1–8 hours) than with immediate release oxymorphone (within 1–4 hours); and (2) the body has multiple opportunities to recirculate the opioid through the bile duct, liver and intestines, producing multiple high-points in blood concentration levels. This multiple peaking is not possible with immediate release oxymorphone because the drug simply does not remain concentrated in the body long enough to be circulated multiple times and produce multiple peaks. Thus, the peak limitations of the '216 Patent do not merely recite natural processes, but instead recite the unnatural result of the body's prolonged exposure to oxymorphone, made possible only because of the inventiveness of the dosage form.

Dr. Banakar also challenged the metabolite limitations of the asserted claims. As discussed in the claim construction section of this decision, the asserted claims of the '216 Patent contain limitations stating that the formulation will “provide[] detectable blood plasma levels of 6-OH oxymorphone [the metabolite] and oxymorphone,” and that ratio of 6-hydroxy-oxymorphone [the metabolite] to oxymorphone in the bloodstream will be between about 0.5 to 1.5. *See, e.g.*, '216 Patent cls. 1, 42, 62 and 64 (incorporating Claim 55). Dr. Banakar argued that these limitations merely recite the inevitable—that once oxymorphone is administered to a patient, that patient's blood will invariably exhibit detectable levels of oxymorphone *and* its metabolite, and always within the ratio claimed. *See* Trial Tr. at 1594:20–23. Thus, Dr. Banakar asserts that the metabolite limitations merely record natural processes. *Id.* at 1594–95.

Again, the court believes that Dr. Banakar's conclusion is unsound. It goes

without saying that the liver's ability to metabolize substances is a natural process. But Endo did not attempt to patent the operation of the human liver, much less the operation of the liver on a natural substance. Rather, Endo patented the myriad of pharmacokinetic effects that occur when a subject ingests the inventive formulation of the semi-synthetic opioid oxymorphone in a controlled-release delivery system. These effects do not occur in the absence of the controlled-release dosage form constituting the invention, and are therefore not natural phenomena.

2. The Pharmacokinetic Limitations Were Not Otherwise Disclosed in the Prior Art.

Defendants argue that even if the pharmacokinetic limitations are not invalid as claiming natural phenomena, they are nonetheless disclosed in the prior art. Defendants assert numerous pieces of prior art to this effect: the Maloney Reference, the Oshlack Reference, the Baichwal Reference, the '912 Patent, the Penwest Reference, and an article published in 2000 in the journal "Cancer Control." See James F. Cleary, *Cancer Pain Management*, 7 *Cancer Control* 120 (Mar. 2000) (DTX-1951) (the "Cleary Reference"). The court must determine whether these references teach the pharmacokinetic characteristics for oxymorphone claimed in the '122 and '216 patents.

The first pharmacokinetic limitation of the asserted claims is that the dosage form containing oxymorphone or its salt will prove analgesically effective, meaning provide a painkilling effect, for twelve hours. See '122 Patent at cl. 1; '216 Patent cl. 1(iv); *see also supra* Part A(1)(a)–(b).

None of the prior art references taught the analgesic effectiveness of

oxymorphone over a twelve-hour period. Maloney taught the analgesic effectiveness of a different molecule, oxycodone, but gave no indication of oxycodone's dosing interval. *See generally* Maloney Reference. Maloney did list the *in vitro* dissolution rate for oxycodone over twelve hours, *id.* at Table 2, and from this it is possible that a person of ordinary skill in the art could infer that oxycodone would have sustained analgesic effects given that much of the drug remained undissolved during that period. But this does not indicate the dosing interval of sustained release oxymorphone.

The same is true of the other prior art references, which show dissolution, and in some instances sustained analgesia, for molecules other than oxymorphone. *See* Oshlack Reference at 14–25 (chlorpheniramine, morphine, oxycodone, hydromorphone, dilaudid, tramadol, and stearyl alcohol); Baichwal Reference Figs. 1–3 (showing both dissolution and pharmacokinetic profiles over twelve hours for the albuterol); '912 Patent Figs. 1–5 (showing analgesic effect and blood plasma concentrations over twelve hours of oxycodone); Webster Reference at 3 (morphine sulfate). The Cleary Reference, published in 2000, indicated that oxymorphone is “currently under development in sustained-release formulation[]” but gives absolutely no indication of dosing interval or twelve-hour efficacy. *See* Cleary Reference at 126.

In short, none of the prior art asserted would give any indication to a person of ordinary skill that *oxymorphone*, as opposed to some other substance, could be developed into a controlled-release formulation providing effective analgesia over a twelve-hour period.

Nor did any of the prior art references disclose the claimed food effects. In fact, defendants made no attempt at trial to show some teaching in the prior art of the food effects of controlled-release oxymorphone. Instead, they merely asserted that those effects were natural processes. And while immediate release oxymorphone's significant food effect is now known, it does not appear to have been known before 2001. *See, e.g.*, Physician's Desk Reference, Twenty-Third Edition (1969) at 698 (DTX-2890) (failing to indicate whether immediate release oxymorphone should be taken under fed or fasted conditions). Furthermore, there was no disclosure in the art that developing oxymorphone into a controlled release formulation would actually improve on immediate release oxymorphone's food effect as measured by AUC, *see supra* Part B(1)(a)(iii)(1), or predict the difference in AUC and C_{\max} values claimed for fed and fasted conditions. *See, e.g.*, '122 Patent cl. 20.

The prior art also failed to teach the multiple peaks in blood concentration levels exhibited by controlled-release oxymorphone. At trial, Dr. Banakar testified that the prior art showed multiple-peaking for controlled release morphine and hydromorphone. *See* Trial Tr. at 1576–77. An article published in 1980 shows multiple peaks in controlled release morphine over a twelve hour period. *See* Leslie *et al.*, *Controlled Release Morphine Sulfate Tablets-A Study in Normal Volunteers*, 9 Br. J. Clin. Pharmac. 531, 534 (1980) (DTX-2816). Likewise, a patent issued in 1991 shows peaks in blood concentration levels of controlled release hydromorphone over twenty-four hours. *See* United States Paten 4,990,341 (the "Goldie Reference") at 8:20–30. But these sources did not

indicate whether *oxymorphone*, when housed in a controlled release setting, would exhibit multiple peaks.

The fact that two controlled-release opioids exhibit multiple peaks does not indicate that a wholly different controlled-release opioid will also exhibit multiple peaks. A defense expert, Dr. Mayersohn, baldly testified that “it is well established for a lot of opioids that you see multiple peaks,” Trial Tr. at 1740:19–20, but he gave no indication of which of the nearly 70 opioids were known to do so in 2001. Unless a significant portion of all opioids were known to exhibit multiple peaks when developed into a controlled release formulation—something defendants did not come close to establishing at trial—there would be no reason for a person of ordinary skill in the art to think that *oxymorphone* would exhibit multiple peaks when developed into a controlled-release formulation. And while Endo certainly knew that *oxymorphone* in immediate release formulation exhibited dual peaks, see ’216 Patent at Fig. 5, such information was not shown to be available to the public. Defendants simply failed to show how the known multiple-peaking of two controlled release opioids indicated multiple peaking for controlled-release *oxymorphone*.

Finally, defendants did not provide prior art disclosing the metabolite limitations of the Endo patents. At trial, defendants were quick to note that it was known that *oxymorphone*, when metabolized by the liver, produced detectable levels of 6-OH *oxymorphone*. See Trial Tr. at 1591. But where Endo claimed as a limitation “detectable blood plasma levels of 6-OH-*oxymorphone* and *oxymorphone*,” it did so only in the conjunctive sense along with four other

limitations for the metabolite. See '216 Patent cl 1(i)-(v). Thus, while it was known that oxymorphone when metabolized produced 6-OH oxymorphone, see Cone *et al.*, *Oxymorphone Metabolism and Urinary Excretion in Human, Rat, Guinea Pig, Rabbit, and Dog*, 11 Drug Metabolism and Disposition 446, 446 (DTX-3554), the prior art taught neither the ratio of oxymorphone to its metabolite, nor the timing of peak metabolite levels, as required by the asserted claims. See '216 Patent cl. 1 (ii)-(iii).

3. Defendants' Convolution Analysis is Irrelevant Because it Relied on Data Not Found in the Prior Art.

In an effort to show the obviousness of the pharmacokinetic effects claimed in the '122 and '216 patents, defendants called a professor of pharmaceutical sciences, Dr. Michael Mayersohn, to testify that a person of ordinary skill in the art in 2001 could use a technique known as "convolution analysis" to predict the pharmacokinetic properties of controlled-release oxymorphone. Trial Tr. at 1706, 1713. The convolution analysis is a three-step process involving: (1) taking the "known" pharmacokinetic properties of immediate release oxymorphone; (2) taking the dissolution profile of known extended release opioids such as morphine; and (3) using computer modeling to combine the first and second steps and predict the pharmacokinetic properties of controlled-release oxymorphone. See Trial Tr. at 1721-23.

Dr. Mayersohn's convolution analysis was flawed from the outset because in 2001 there was no publicly available source disclosing the pharmacokinetic properties of immediate release oxymorphone. At trial, Endo's former chief

scientific officer, Dr. David Lee, testified that when Endo began developing oxymorphone into a controlled release formulation, there was a lack of published research on immediate release oxymorphone's pharmacokinetic properties. *See* Trial Tr. at 202. Although the FDA had approved oxymorphone for sale as the branded drug Numorphan in 1959, it did not at that time require efficacy data. *Id.* at 203:2. In fact, in 2001 there had been only four published studies on oral oxymorphone. *See* Briefing Packet (PTX-0223 at 410). Endo's project development team realized that oxymorphone was for all intents and purposes a "pharmacologic enigma." Trial Tr. at 203:11.

It was Endo's own development team that, beginning in 1998, performed the studies needed to measure immediate-release oxymorphone's pharmacokinetic effects. *See, e.g.,* EN3202 Project Team Minutes (6/26/98) (PTX-173 at 342627) (discussing the results of an eight-subject pilot pharmacokinetic study). It was only after Endo had studied the pharmacokinetic properties of immediate release oxymorphone that it could take the next step, and begin developing controlled release oxymorphone. *See* Trial Tr. at 197–99.

All of Endo's studies on immediate-release oxymorphone's pharmacokinetic effects were confidential, and as defendants' own expert testified, "not available in the literature." Trial Tr. at 1741:10–11; *see also* Excerpt from Endo Study EN3203-001 (DTX-1069A). But when Dr. Mayersohn performed his convolution analysis, he used Endo's information as a starting point. *See* Trial Tr. at 1758:1-4 ("Q. The study . . . which you relied on for oxymorphone pharmacokinetic profile data is an Endo study, right? A. Yes, sir.").

His only alternative would have been to conduct his own pharmacokinetic study, which he suggested could have been done by enlisting “six to perhaps ten human subjects.” Trial Tr. 1741:18–19.

The court finds Dr. Mayersohn’s testimony to be unpersuasive. Regardless of whether convolution analysis can be used to predict the pharmacokinetic effects of a new controlled release drug, it requires as its starting point pharmacokinetic data for the immediate release formulation. In performing his convolution analysis, Dr. Mayersohn used Endo’s own pharmacokinetic data, information that would be unavailable to the public in 2001, and which simply does not constitute “prior art.” Dr. Mayersohn’s suggestion that an ordinarily skilled artisan could perform his own study to obtain such data misses the point. The fact is that there was no published source in 2001 disclosing the relevant pharmacokinetic properties of immediate release oxymorphone. Therefore, a person of ordinary skill in the art would have lacked the information necessary to perform a convolution analysis predicting the pharmacokinetic properties of controlled-release oxymorphone.

iv. Whether Secondary Considerations Indicate the Non-Obviousness of the Invention.

The final factor in the obviousness inquiry asks the court to consider objective indicia of non-obviousness, including the commercial success of the invention, the invention’s satisfaction of a long-felt but unmet need, the failure of others to solve the problem at hand, and the copying of the invention by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

Endo was persuasive in demonstrating the commercial success of its

OPANA®ER products, and in relating the success of those products to the claims of the '122 and '216 patents. Endo's expert on commercial success, economist Dr. Gregory Bell, demonstrated that once OPANA®ER launched in 2006, it gained wide acceptance among physicians, going from zero prescriptions before launch to 350,000 prescriptions in 2011. Trial Tr. at 1994:1–2. During the same period, gross sales of OPANA®ER increased by a corresponding amount, from zero dollars in 2006 to well over \$150 million in 2011. See PTX-0336 (showing IMS sales data by month). OPANA®ER achieved this growth despite facing competition from other long-acting opioids, including branded and generic morphine, methadone, and oxycodone. Trial Tr. at 1990–91. Since its launch in 2012, OPANA®ER CRF has experienced consistent sales, despite the entry of Actavis's generic tablets on the market. *Id.* at 1995.

In cross-examining Dr. Bell, defendants attempted to establish that OPANA's commercial success was more the result of aggressive advertising and rebate programs than the drug's inherent properties. Trial Tr. at 2046–48. But Dr. Bell demonstrated, to the court's satisfaction, a clear nexus between the asserted claims of the '122 and '216 patents and the market success of the branded product. As discussed at length in the preceding sections of this decision, key features of the invention include its twelve-hour dosing interval and analgesic effectiveness over the same period. When physicians were asked why they were prescribing OPANA®ER, they overwhelmingly attributed their decision to clinical properties such as the drug's ability to provide "effective pain relief," "good side effect profile" and "long duration of action." See Trial Tr. at

2012–13, *see also* PX4010.15 (showing the results of a physician survey). Physicians also cited other reasons attributable to the invention, including better tolerability and greater pain relief. *See* PX4010.15. Thus, the court is satisfied that OPANA®ER has achieved commercial success, and that there is a nexus between that success and the asserted claims of the '122 and '216 patents.

The court is also persuaded that the invention satisfied a long-felt but unmet need in the marketplace. Endo's expert on long-felt need, Dr. Edgar Ross, testified that the medical community had long sought additional tools to effectively combat chronic pain. *See* Trial Tr. at 935–37. At the time of the invention, there were numerous immediate release opioids on the market, but these had a short duration and often involved inconvenient routes of administration, such as intravenous and transdermal delivery. Trial Tr. at 941–42. Three controlled release opioids, morphine, methadone, and oxycodone, were on the market, but exhibited negative effect in some patients, including causing nausea and vomiting, poor interaction with other drugs, and diminished analgesic potency in patients unable to produce certain enzymes. Trial Tr. at 949–50. Overuse of the existing opioids could also result in increased tolerance, requiring physicians to either increase the dose, risking toxicity, or alternatively switch patients to a different opioid (opioid rotation). Trial Tr. at 952. The introduction of a new controlled-release opioid, oxymorphone, fulfilled the need for a drug with less side effects than those currently on the market, and the need for an additional option for use in opioid rotation. *Id.* at 952–53.

Others had failed to develop oxymorphone into a controlled release setting

before Endo, but have since copied that work. Endo developed OPANA®ER between 1997 and 2001, and launched it in 2006. Trial Tr. at 794:18–21. It was undisputed at trial that no entity had developed oxymorphone in an extended release formulation before then. It was only after OPANA®ER had demonstrated years of significant growth in sales and prescriptions that other companies decided to develop their own sustained-release oxymorphone products. *See* Trial Tr. at 1994:1–2. Indeed, the instant litigation involves attempts by generic drug manufacturers to do exactly that.

OPANA®ER experienced significant commercial success in the years following its launch despite the existence of branded and generic opioid competition. There was a clear need for an additional opioid for use in opioid rotation, as well as one that would be better tolerated by patients ill-disposed to morphine, methadone, and oxycodone. Finally, it is undisputed that no other entity had developed controlled-release oxymorphone before Endo, and that others only did so years after the drug's commercial success had been established. These secondary considerations indicate that the invention was non-obvious.

b. Whether the On-Sale Bar Applies.

Defendants argue that the '122 and '216 patents are invalid because the invention was ready for patenting and the subject of a commercial offer for sale more than a year before the patent applications were filed on October 15, 2001.

At trial, defendants' expert on the on-sale bar, Dr. Anthony Palmieri, testified that all of the dissolution and pharmacokinetic studies necessary to

achieve the claimed invention were performed before August of 2000. See Trial Tr. at 2307. Dr. Palmieri showed that for one dosage strength (20mg), OPANA®ER's formulation was determined as early as July of 1998. Trial Tr. at 2283. Moreover, Endo had completed a study on the *in vitro* dissolution rate of the tablets by October of that year. See EN3202 Formulation Development Report Part A EN3202 (PTX-0149 at 0634). Studies showing the dissolution and pharmacokinetic characteristics of the drug were performed by March of 2000. See, e.g., Trial Tr. at 2290:16–18.

Finally, Dr. Palmieri testified that Endo knew the twelve-hour analgesic effect of its product by August of 2000. Trial Tr. at 2307. To support this assertion, Dr. Palmieri pointed to minutes from an August meeting between Endo and Penwest discussing the “preliminary results” from a study, study fifteen, showing that “EN3202 [OPANA] is an effective analgesic.” See EN3202 Alliance Committee Meeting Minutes (Aug. 21, 2000) (PTX-589 at 7886–87) (emphasis in original). These “preliminary results” were again discussed at a meeting of Endo’s Project Team in September of 2000. See EN2302 Project Team Meeting Minutes at 1 (Sept. 14, 2000) (PTX-345) (“preliminary results are positive. . . EN3202 is an effective analgesic.”).

Endo’s expert, Dr. Edgar Ross, disputed the notion that the invention was ready for patenting before October 15, 2000. He explained that even though many of the studies on OPANA®ER (project name EN3202) had been completed before then, only the preliminary reports were available for some of them. Trial Tr. at 2816. Dr. Ross explained that preliminary reports cannot be completely

trusted until the data from the study is carefully scrutinized and memorialized in a final report. Trial Tr. at 2816. In the interim, results may change significantly if errors are discovered. *Id.*

The final report for study fifteen, which defendants suggested was completed in August of 2000, was not in fact issued until June 19, 2001. See *generally* Final Clinical Study Report, Double-Blind, Placebo Controlled . . . Comparison of the Efficacy and Safety of Controlled Release Oxymorphone (PTX-271). A final report for a study measuring controlled oxymorphone’s “steady state” blood concentration levels was not issued until August 14, 2001. See A Randomized, Two-Period Crossover Trial Comparing the Single-Dose and Multiple-Dose (Steady State) Pharmacokinetics and Bioavailability of Numorphan CR and Numorphan IR Tablets Phase I (PTX-281).

The evidence does not demonstrate that the invention was ready for patenting more than a year before the applications were filed. As discussed in the claim construction section of this decision, a primary feature of the invention is that the dosage form will be “analgesically effective” for twelve hours, meaning it provides pain relief for that period. See *supra* Part A(1)(a). The invention could not be reduced to practice until the inventors were certain that it would provide the claimed analgesic effect. While preliminary reports indicated OPANA®ER’s analgesic effectiveness, those results were not sufficiently trustworthy until the study data had been fully scrutinized. In the end, a mere two months separated the finalization of study nine, and just four months separated the finalization of study fifteen, from the filing of the ’122 and ’216 patent applications. Thus, the

court concludes that the invention was not ready for patenting before the “critical date.”

Furthermore, the invention was not the subject of a commercial offer for sale before October 15, 2000. In June of 2000, Endo entered into a “Development and Clinical Supply Agreement” with drug manufacturer Novartis Consumer Health Inc. See Development and Clinical Supply Agreement at 1 (June 1, 2000) (PTX-347). The stated purpose of this agreement was for Novartis to manufacture tablets for Endo [REDACTED] *Id.* This was not a commercial offer for sale. To the extent a supply agreement could even be considered a “sale,” the transaction was clearly experimental in nature, not commercial. *Id.* Because an NDA filing requires demonstrating to the FDA a drug’s safety and efficacy, the “sale” of tablets for [REDACTED] will involve human and laboratory testing, clearly an experimental purpose. Indeed, the agreement explicitly assumes that [REDACTED]

[REDACTED] Since the Development and Supply Agreement involved a sale for [REDACTED], the court concludes that it was experimental in nature.

Because the invention was not ready for patenting nor the subject of a commercial offer for sale before October 15, 2000, the on-sale bar does not apply.

c. Whether the '122 and '216 Patents Satisfy the Requirements of 35 U.S.C. § 112.

Defendants argue that the '122 and '216 Patents fail to satisfy the definiteness, enablement, and written description requirements of 35 U.S.C.

§ 112(a).

With regard to definiteness, the court concludes that the claims give adequate notice of the metes and bounds of the invention. As discussed, there was some debate at trial over the definition of “peaks” at trial. The court viewed this debate as one primarily of construction, but it could be argued that the Endo patents’ call for multiple “peaks,” and to a lesser extent “detectable blood plasma levels,” *see, e.g.*, ’216 Patent at 26:35–55, would leave a skilled artisan in some doubt as to how those limitations could be satisfied. But as discussed, the definition of the term “peak” would be readily apparent to a person of ordinary skill in the art upon reading the specification. *See supra* Part A(1)(b). Moreover, the specification provides that the studies described in the patents were performed using “standard FDA procedures such as those employed in producing results for use in a new drug application.” ’216 Patent at 3:63–65. From this, an ordinarily skilled artisan would have known how to detect blood plasma levels of oxymorphone.

With regard to written description and enablement, the court concludes that the patents would reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date, and that such artisans would be able to make and use the invention without undue experimentation. Each of the features recited in the patent claims, such as an “oral controlled release oxymorphone formulation” of “about 5mg to about 80mg of oxymorphone” finds adequate, even abundant, support in the specification. *Compare* ’216 Patent cl. 1 with ’216 Patent at 4:37–40. Moreover, the patent

specifications are replete with examples of dosage forms satisfying each of the claimed limitations. *See, e.g.,* '216 Patent at 13–14. For example, the specification describes the administration to subjects of tablets containing 20mg of controlled-release oxymorphone, '216 Patent at 13:59–61, which were then shown to produce dissolution and pharmacokinetic characteristics within the ranges claimed. *Id.* at 14:59–15:20. The specifications also give detailed descriptions of the *in vitro* and *in vivo* testing methods employed in developing the tablets. *Id.* at 3–4. A person of ordinary skill in the art, upon reading the specifications, would be convinced that Endo possessed the invention claimed, and could also use the specification to develop his own tablets constituting the invention.

At trial, defendants' expert on indefiniteness, Dr. Arthur Kibbe, testified that certain of the asserted dissolution claims are overbroad. Trial Tr. at 1884–85. To wit, the specification shows the *in vitro* dissolution rate of three different formulations of OPANA®ER. *See* '122 Patent Table 4. The slowest-dissolving tablet had dissolved 27.8% after the first hour, and the fastest-dissolving tablet had dissolved 32.3% after the first hour. *Id.* However, when Endo wrote its dissolution claims, it recited a broader dissolution range of 15%–50% at one hour. *See, e.g.,* '122 Patent cl. 19. It recited similarly broad ranges at the four and ten hour marks. *See* Trial Tr. at 1891:5–13. In Dr. Kibbe's view, these broad ranges indicate that the claims are insufficiently described in the specification. *See* Trial Tr. at 1879.

Defendants have not persuasively shown that the dissolution claims are

so broad as to fail to inform an artisan that Endo possessed the invention claimed. A person of ordinary skill in the art, upon reading the dissolution ranges, would understand that the inventors had chosen ranges encompassing the invention, and also allowing for variations. Indeed, had the claims been more restrictively drawn they would have invited infringement. If, for example, Endo had claimed a dissolution range at the first hour of 27%–33%, generic manufacturers could escape infringement by formulating a tablet that dissolves at 26% percent at one hour, or that dissolves at 34% at one hour. The ordinarily skilled artisan, upon reading broader claims, would understand them to encompass the invention as claimed and possessed by the inventor.

The court concludes that the asserted claims, including the dissolution claims, would convey to those skilled in the art the metes and bounds of the invention and that Endo possessed the invention as claimed. Moreover an artisan, upon reading the claims and specifications, would be able to formulate his own controlled-release oxymorphone tablets. Thus, the '122 and '216 patents satisfy the written description, enablement, and definiteness requirements of 35 U.S.C. § 112.

Conclusion Regarding the Validity of the '122 and '216 Patents

Defendants have failed to show, by clear and convincing evidence, that the '122 and '216 patents are invalid. Defendants did not assert that the patents are anticipated. With regard to obviousness, the art revealed no motivation to select oxymorphone for use in a controlled-release formulation, and it failed to disclose the matters recited in the asserted claims. Even if an artisan were somehow

motivated to select oxymorphone for use in a controlled release setting, he would have no reasonable expectation of success in doing so given the failure of the art to disclose the pharmacokinetic and dissolution characteristics. Moreover, secondary considerations strongly indicate the invention's non-obviousness. Because defendants' other defenses are without merit, the court concludes that they have failed to carry their burden and have not shown, by clear and convincing evidence, that the '122 and '216 patents are invalid.

2. Whether the Asserted Claims of the '060 Patent are Invalid.

Defendants also challenge the validity of the final patent-in-suit, the '060 Patent. Abuse-deterrence is the primary feature of the invention embodied in the '060 Patent, and is achieved through the tablet's exceptional hardness and its ability to accommodate secondary barriers. As discussed, Endo licensed the '060 Patent from co-plaintiff Grünenthal in order to develop OPANA®ER into a crush-resistant formulation. Endo and Grünenthal now assert infringement of the '060 Patent by those defendants seeking approval to market crush-resistant oxymorphone tablets. Crucial to the instant litigation, then, is whether defendants have carried their burden in showing the '060 Patent to be invalid.

The '060 Patent reflects research and development performed by Grünenthal and its former head of pharmaceutical development, Dr. Johannes Bartholomäus. Grünenthal began exploring abuse-deterrent technologies in response to the growth in the abuse of prescription opioids, including the widespread abuse of OxyContin in the United States. *See* Trial Tr. at 984. Early on, Dr. Bartholomäus tested a number of ideas for combatting tablet abuse,

including the use of antagonists which block the action of the opiate in the body. See Trial Tr. at 989:22–24; 993:3–5. However, Grünenthal found each of these solutions to be inadequate.

In November of 2002, Dr. Bartholomäus gave a presentation suggesting the company explore other ways to combat abuse, such as making the tablets harder. See Trial Tr. at 999–1000. He suggested using PEO to “increase [the] mechanical resistance of tablets.” Presentation at 19 (Nov. 11, 2002) (PTX-2199). After the presentation, Dr. Bartholomäus put this idea to work in the laboratory, making tablets solely out of compressed PEO. Trial Tr. at 1006. Those tablets proved to be exceptionally strong and resistant to crushing. Trial Tr. at 1007. However, the strength of the tablets evaporated when Dr. Bartholomäus added an opiate to them. *Id.* Adding the opiate seemed to “destroy” the hardness conferred by the PEO. *Id.*

Dr. Bartholomäus went on to conduct further experiments on mixtures of PEO and opiates. Eventually, he realized that by heating the mixture and forming it using a die and punches, he could create an opioid/PEO tablet of exceptional hardness. Trial Tr. at 1008–10. Not only was the tablet exceptionally hard, able to withstand 500N of pressure, it also dissolved in conditions mimicking the human body, releasing the opioid. Trial Tr. at 1011:11–15. Upon showing this to his managers, Dr. Bartholomäus set out to develop a process to mass produce the tablets. Trial Tr. at 1015:21–22. Over the next year, he and another inventor, Dr. Elisabeth Arkenau, did just that. Trial Tr. at 1016:14–16. Their work ultimately resulted in the '060 Patent.

Defendants argue that the '060 Patent is invalid for three reasons: (a) previous decisions of this court have a collateral effect establishing the invalidity of the asserted claims; (b) a prior art reference known as the McGinity Application anticipates the asserted claims; and (c) the asserted claims would have been obvious to a person of ordinary skill in the art at the time of the invention. The court will address each of these arguments in turn.

a. The Collateral Effect of This Court's Prior Decisions.

Defendants argue that a prior case in this court preclusively establishes that a piece of prior art known as the McGinity Application anticipates the asserted claims of the '060 Patent.

The "McGinity Application" is a patent application filed in 1997 by James McGinity and others to the World Intellectual Property Organization. See International Patent Application Publication WO 97/49384 (DTX-0098 at 2408) (the "McGinity Application"). The McGinity Application teaches the creation of controlled-release drugs using hot-melt extrusion. *Id.* at 11. Hot melt extrusion occurs in three steps consisting of combining a powdered-therapeutic compound with PEO and other optional components; and placing the mixture in an "extruder hopper" which is heated to a temperature that will melt or soften the PEO. The softened mixture then exits the extruder through a die; and still warm, is shaped, molded, chopped, cut, or tableted into the desired physical form. *Id.* at 11:28–30.

In addition to asserting the '060 Patent in this litigation, Grünenthal had also initially asserted two other patents, United States patent numbers

8,114,383 (the “’383 Patent”) and 8,192,722 (the “’722 Patent”). Grünenthal’s assertion of the ’383 Patent was significant because it had asserted that same patent in a different case before this court involving the prescription drug OxyContin. In 2014, following a month-long bench trial, Judge Stein issued a decision concluding that the asserted claims of the ’383 Patent were invalid as anticipated by the McGinity Application. *See In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d 367, 424 (S.D.N.Y. 2014).

In light of Judge Stein’s decision, defendants in these actions filed a motion for partial summary judgment, arguing that the decision precluded Grünenthal from litigating the asserted claims of the ’060, ’383, and ’722 patents here. *See* Dkt. No. 70, *Endo Pharmaceuticals Inc. et al v. Actavis Inc. et al.*, No. 13-CV-00436. The undersigned agreed in part, recognizing that Judge Stein had expressly invalidated (as anticipated by McGinity) four of the five asserted claims of the ’383 Patent, and that his decision precluded litigation of those claims here. *See* Opinion of March 17, 2015 at 4 (Dkt. #117 in Case 13-cv-00436) (the “March 17th Opinion”). The court also recognized a collateral effect with regard to the final asserted claim of the ’383 Patent. *See id.* at 5. However, the court held that there was no collateral effect with regard to the ’060 Patent because that patent was never asserted before Judge Stein and, more importantly, recited limitations concerning abuse-deterrence absent from the adjudicated claims of the ’383 Patent. *Id.* at 6–7.

Although the undersigned had rejected their collateral estoppel theory with regard to the ’060 Patent, defendants continued to press the argument at trial,

arguing that the similarities between the '383 Patent and the '060 Patent are so pronounced as to require a preclusive effect. *See* Trial Tr. at 135–36. *See also* Side By Side Comparison (DX-9001).

The court finds no need to revise its holding regarding the OxyContin decision's lack of a preclusive effect on the asserted claims of the '060 Patent. As the undersigned noted in the March 17th Opinion, there are “intriguing similarities” between the '383 and '060 patents. However, the '060 Patent has a crucial difference: it describes an *abuse-proofed* dosage form. *See* '060 Patent Claim 1. All of the asserted claims of the '060 Patent share this limitation. *See* '060 Patent cls. 4, 9, 24, 25, 27, 29, 30, 31, 32, 33, and 34 (all depending from Claim 1 or from claims themselves depending therefrom). Moreover, Claim 9 of the '060 Patent recites six additional barriers to abuse. '060 Patent at 21:37–51. In contrast, the asserted claims of the '383 Patent made no mention of abuse-proofing, nor did they recite additional barriers to abuse. *See* '383 Patent at 21–22. Thus, Judge Stein made no findings or conclusions as to whether an “abuse-proofed” dosage form would be invalid in light of the prior art, either through anticipation or obviousness. Consequently, the undersigned will not revise the holding that Judge Stein's decision regarding the '383 Patent does not preclude litigation of the asserted claims of the '060 Patent here.

b. Whether the Asserted Claims Are Anticipated by the McGinity Application.

Defendants argue that the McGinity Application anticipates the asserted claims of the '060 Patent. A prior art reference anticipates—and invalidates—the asserted claims only if it expressly or inherently discloses each of the invention's

claimed elements. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). The primary element of the asserted claims of the '060 Patent is that the tablets will be “abuse-proofed,” *see* '060 Patent cl. 1, meaning they reduce the potential for abuse, by among other things exhibiting exceptional hardness. *See supra* Part (A)(1)(c)(i).

The McGinity Application is silent regarding abuse reduction. It describes the process of hot-melt extrusion, but does not say whether the process could produce abuse-proofed dosage forms or even dosage forms of unusual strength. Indeed, the words “abuse,” “crush,” “hardness,” “breaking,” “strength,” “newtons,” “snort,” “inject,” “insufflate,” etc... are wholly absent from the McGinity Application. Thus, the McGinity Application, while teaching a process for creating controlled-release tablets using hot-melt extrusion, fails to expressly disclose abuse-proofing.

In order to show anticipation, then, it was incumbent on defendants to prove at trial that abuse-proofing is inherent to tablets made pursuant to the McGinity Application. To this end, Defendants’ expert on invalidity, Dr. Fernando Muzzio, testified that any tablet made using the process described in the McGinity Application would be “abuse-proofed” because it would be exceptionally hard. *See* Trial Tr. at 2164–65. Dr. Muzzio tested this theory in the laboratory. He read the experiments disclosed in the McGinity Application and made tablets replicating those experiments. Trial Tr. at 2168. He then inserted his “McGinity tablets” into an Instron testing devise and determined their breaking strength. *Id.* None of the tested tablets broke when subjected to

pressures above 500N. See Excerpt of the Final Muzzio Report at 36, (DTX-5119A). Indeed, video presented at trial showed that the McGinity tablets remained entirely whole. Thus, Dr. Muzzio concluded that tablets made pursuant to the McGinity Application are inevitably hard, and thus inevitably resistant to abuse through crushing.

The court is not persuaded that the McGinity Application inherently discloses abuse-proofing. In order to have an “abuse-proofed tablet,” the tablet must contain an ingredient that is known to have abuse potential, such as the oxymorphone in plaintiffs’ tablets. Indeed, McGinity discloses that the invention can be used with analgesics. See McGinity Application at 8:20-35. Some analgesics, notably opioids, were known to have abuse potential. But in creating his tablets, Dr. Muzzio did not use an opioid or any other active ingredient with abuse potential. Rather, Dr. Muzzio created his McGinity tablets using the cancer drug chlorpheniramine maleate (“CPM”). Trial Tr. at 2496:3; *see also* Expert Report of Fernando J. Muzzio, Ph.D. Ex. B at 2 (DTX-5119A) (“All of the formulations to be tested in this work are composed of . . . Chlorpheniramine Maleate.”). Chlorpheniramine maleate, as Dr. Muzzio conceded at trial, is not known to have abuse potential. Trial Tr. at 2200:22–23.

The court can only speculate as to why Dr. Muzzio, in attempting to show that the practice of the McGinity Application would inevitably result in abuse-proofed tablets, chose to use an active ingredient that is not prone to abuse. Perhaps he felt confined to the active ingredient actually used in McGinity’s examples. See McGinity Application at 19 (using CPM). But as Dr.

Bartholomäus's early experiments with PEO showed, the introduction of a novel ingredient can dramatically alter PEO's hardness-conferring properties. Trial Tr. at 1006-07 ("I saw from this that mixing and adding this opiate . . . with this polyethylene oxide, this PEO, does destroy any properties that PEO might have to form a high crushing strength tablet."). This is confirmed by McGinity, which expressly teaches that "particular combinations of therapeutic compound and PEO (of given molecular weight) will result in various formulations each possessing its particular combination of properties." McGinity Application at 3:15-17.

If Dr. Muzzio wished to establish that McGinity tablets are inevitably abuse-proofed because of their hardness, he should have used an active ingredient known to have abuse potential, such as an analgesic. Because he did not do so, he merely succeeded in showing that hot-melt extrusion of PEO and chlorpheniramine maleate ("CPM") will result in hard, even astoundingly hard, tablets. See Muzzio Report at 35 (DTX-5119a) (showing breaking strengths between 2,000 and 4,500 newtons). But such tablets cannot be said to be abuse-proofed because they have no ingredient with abuse-potential.

Moreover, the McGinity application is silent with regard to the type of additional barriers to abuse contained in Claim 9 of the '060 Patent. See '060 Patent at 21:37-51. It does not disclose irritants, viscosity increasing agents, antagonists, emetics, dyes, or bitter substances as required by the claim.

Dr. Muzzio's tests clearly demonstrate that the process taught in the McGinity Application, the hot-melt-extrusion of PEO and a therapeutic

compound, will result in exceptionally hard tablets, and this demonstration is significant to the court's obviousness analysis. But given Dr. Muzzio's decision to use an active ingredient without abuse potential, the court feels that defendants fall slightly short of carrying their burden in showing anticipation.

Defendants have not persuasively shown that McGinity inherently discloses abuse-proofing, and neither have they shown that McGinity discloses the additional barriers to abuse recited in Claim 9. Thus, the court concludes that defendants have not carried their burden in showing that the McGinity Application anticipates the asserted claims of the '060 Patent.

c. Whether the Asserted Claims of the '060 Patent Would Have Been Obvious to a Person of Ordinary Skill in the Art at the Time of the Invention.

The next step in determining whether the '060 Patent is invalid is to consider whether the asserted claims of the '060 Patent would have been obvious, in light of the prior art, to an ordinarily skilled artisan in 2003.²⁰ At trial, the parties identified three areas in dispute regarding the obviousness of the invention: (i) whether there was a motivation in the prior art to develop unusually hard tablets as a means of reducing the abuse of opioids; (ii) whether the prior art discloses the limitations of the asserted claims of the '060 Patent; and (iii) whether secondary considerations indicate the invention's non-obviousness.

i. Whether There Was a Motivation to Make Unusually Hard Tablets as a Means of Reducing Opioid Abuse.

²⁰ As a divisional application of the '383 Patent, the '060 Patent is entitled to that patent's filing date for obviousness purposes. *See* 35 U.S.C. § 120.

Defendants argue that there was a motivation in the art to make unusually hard tablets as a means of reducing opioid abuse. See Trial Tr. at 2187–88. Defendants rely on three patents to support this assertion: United States Patent Number 7,968,119 (the “’119 Patent”); United States Patent Number 6,696,088 (the “’088 Patent”); and United States Patent Number 7,33,182 (the “’182 Patent”). The applications for each of these patents were filed before 2003. Defendants also rely on a body of art from 2002 related to the branded stimulant Concerta.

The ’119 Patent shows knowledge in the art of the abuse of narcotics, including opioids and oxymorphone, through crushing and other means. It describes the invention of a “tamper proof system for delivery of narcotics.” See ’119 Patent at 1: 15-18 (DTX-161). It describes combining an active ingredient with an antagonist. *Id.* at 3–4. When the drug is taken properly, the active ingredient will provide the desired effect long before the antagonist is activated. *Id.* at 4:1–9. However, when the dosage form is tampered with, through “adulteration, distillation, or *pulverization*,” the antagonist will be activated and block the euphoric effect of the drug. *Id.* at 4:50–64 (emphasis added). At the same time, tampering will “induc[e] a bowel movement in the subject” resulting in “rapid detoxification.” *Id.* at 3–4.

The ’088 and ’182 patents also show knowledge in the art of opioid abuse through crushing. The ’088 Patent, like the ’119 Patent, uses an antagonist that only activates once the dosage form is “tampered with” by “crushing” or

“shearing.” ’088 Patent at 7:38–40. Similarly, the ’182 Patent suggests using an antagonist, as well as aversive agents (an irritant), to reduce tampering of the dosage form through crushing, shearing, grinding, and dissolving. *See* ’182 Patent at 4:55–59.

These pieces of art show that there was knowledge of opioid abuse through crushing, and thus show some motivation to solve that problem. However, they do not show a motivation to select hardness as the solution. To the contrary, the ’119, ’088, and ’182 patents taught away from selecting hardness as an abuse-deterrent feature because their antagonists are released when the dosage form is pulverized, sheared, crushed or ground. *See, e.g.*, 119 Patent at 3–4. To a person of ordinary skill in the art, patents teaching the use of crush-activated antagonists to deter abuse would not also teach crush-resistance (hardness) as a feature to deter abuse.

Defendants are more persuasive in arguing that the prior art surrounding the branded drug Concerta taught the use of exceptional hardness to deter drug abuse. Trial Tr. at 2189. Concerta is a branded stimulant used in the treatment of Attention-Deficit/Hyperactivity Disorder. *See* Letter to the Editor of the Journal of the American Academy of Child & Adolescent Psychiatry (2002) (DTX-84 at 0759). It uses a technology, OROS, to deter abuse. An OROS tablet is designed to act as an “osmotic pump.” Trial Tr. at 2517:8–9. The outside layer of the tablet consists of a semi-permeable membrane that absorbs water, allowing the inside contents of the tablet (containing the active ingredient and PEO) to be dissolved and slowly pushed out through a hole at the top of the tablet. Trial Tr.

at 2522.

Four pieces of prior art in 2002 indicated that Concerta was known to be hard, and also known to deter abuse through crushing. A magazine article stated that Concerta is “difficult to abuse because . . . in [its] time-release form, [it] can’t be chopped and snorted.” Craig Donnelly, MD., ADHD Medications Past and Future, 22 *Behavioral Health Management* 28, 29 (2002) (DTX-2554). An article in the Sacramento Bee newspaper stated that Concerta’s manufacturer, McNeil, had “released a fact sheet stating that Concerta is hard to abuse because it is difficult to crush.” Dorsey Griffith, *Potential New ADHD Drug Creating Lots of Big Hopes*, Sacramento Bee (Oct. 30, 2002) (DTX-82 at 0754). An article in Child & Adolescent Psychiatry indicated that Concerta is “resistant to diversion (cannot be ground up or snorted), [and] is well suited for treatment of adolescents. Greenhill *et al.*, *Practice Parameter for the Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults*, 41 J. Am. Acad. Child Adolescent Psychiatry (Feb. 2002) (DTX-80 at 0745). Finally, a letter to the editor in the same journal indicated that the ingredient in the “Concerta tablet is very difficult . . . to crush if the tablet is chewed accidentally.” Ciccone, P. E., *Attempted Abuse of Concerta*, Letters to the Editor, J. Am. Acad. Child Adolescent Psychiatry, 41:7 (July 2002) (DTX-100). This significant body of art shows knowledge of hardness as a feature to deter abuse through crushing.

Plaintiffs’ experts dispute Concerta’s teaching. Dr. Bartholomäus testified that he knew of the OROS technology (the tablet technology used in Concerta) in 2002, but didn’t believe OROS tablets to be crush-resistant because his team

“bought some OROS from the U.S. market, took it to Germany, worked on it, and we could crush it. So it didn't solve the problem of crushing.” Trial Tr. at 1000:21–23. Similarly, Dr. Davis testified that OROS was easily subverted by peeling off the outer membrane, “like the skin of an orange,” and that once the outer membrane is removed the tablet becomes “quite soft.” Trial Tr. at 2519: 11-13; 2520:4.

Plaintiffs have not persuasively countered defendants’ assertion that the body of art surrounding Concerta would indicate hardness as a means of deterring abuse. The fact that Dr. Bartholomäus knew of OROS in 2002, and was motivated to test its hardness with a mortar and pestle, indicates that other ordinarily skilled artisans would also be motivated to explore exceptional hardness as an abuse-deterrent feature. Both his and Dr. Davis’s observation that OROS is easily subverted by peeling is irrelevant as to whether a motivation to develop hard tablets was taught by the prior art.

The art surrounding antagonist-based tablets demonstrated a motivation to solve the problem of crushing prescription drugs. The Concerta art made the same observation, and also indicated the use of hardness as a solution. While Concerta’s active ingredient was a stimulant, an ordinarily skilled artisan would readily understand it to teach the abuse-deterrent value of hardness for other active ingredients, including opioids. Thus, the court is persuaded that there was a motivation in the art to solve the crushing of opioids by making tablets of exceptional hardness.

ii. Whether the Prior Art Discloses the Limitations of the Asserted Claims of the ’060

Patent.

At trial, the parties disputed whether the prior art discloses: (1) an abuse-proofed thermoformed dosage form; comprising (2) one or more active ingredients with abuse potential and (3) at least one synthetic or natural polymer with a weight of at least 0.5 million according to rheological measurements; and more specifically the polymer polyethylene oxide; and (4) which exhibits a breaking strength of 500N; and (5) the six additional barriers to abuse recited in Claim 9 of the '060 Patent.

1. The Prior Art Discloses Thermoforming and Abuse Proofing.

The McGinity Application discloses thermoforming. As discussed in the claim construction section of this opinion, a thermoformed dosage form is one created by applying pressure to a mixture of an active ingredient and a high molecular weight polymer and exposing the mixture to the prior, simultaneous, or subsequent application of heat. *See supra* Part A(1)(c)(ii). The McGinity Application describes a dramatically similar process, hot melt extrusion, involving mixing a therapeutic compound with high molecular weight PEO, placing the mixture into an extruder which is heated, and then pushing that mixture through a die. *See* McGinity Application at 11:18–33. These two processes are so similar that at trial, experts for both sides referred to hot-melt extrusion as a type of thermoforming. *E.g.*, Trial Tr. at 1083:25–1084:2 (“Now hot melt extrusion is a type of thermoformed dosage form, yes? [BANAKAR] A. In general, yes”). Because hot-melt-extrusion shares the key features of thermoforming, the court concludes that the McGinity Application discloses a

“thermoformed dosage form” as required by the asserted claims.

Regarding “abuse-proofing,” there is a substantial body of prior art showing that the use of PEO and hot melt extrusion will result in tablets of unusual hardness, thus reducing the potential for abuse by crushing. PEO’s strengthening properties were certainly known. A patent awarded in 1992 provided that “it is preferred to increase the hardness of the excipient by adding a small amount of polyethylene oxide (PEO) having a molecular weight from about 100,000 to about 500,000 daltons. The high molecular weight polyethylene oxide contributes strength to the molded dosage form and reduces brittleness.” See United States Patent 5,139,790 at 5:19–28 (DTX-75). Likewise, a journal article showed that compressed tablets containing PEO in various proportions exhibits a breaking strength up to 255N, see L. Maggi *et al.*, *Dissolution Behaviour of Hydrophilic Matrix Tablets Containing Two Different Polyethylene Oxides (Peos) For The Controlled Release Of A Water Soluble Drug*, 23 Biomaterials 23: 1113, 1119 (2002) (DTX-76), which is above the known breaking strength of regular tablets (100N-200N). See Trial Tr. at Trial Tr. at 1024:13–14; 2528:24.

Hot melt extrusion was also known to increase the strength of tablets. A dissertation published in 1999 by Feng Zhang, co-inventor on the McGinity Application, provided that “hot-melt extrudate is anticipated to possess a higher physical strength . . . than tablets prepared by . . . direct compression.” Zhang, Feng, *Hot-Melt Extrusion as a Novel Technology to Prepare Sustained-Release Dosage Forms* at 69 (DTX-170). Similarly, an article co-authored by Zhang and

McGinity in 2001 provides that “When compared with traditional [melt granulation] HME [hot melt extrusion] produced harder tablets.” Liu *et al.*, *Properties of Lipophilic Matrix Tablets Containing Phenylpropanolamine Hydrochloride Prepared by Hot-Melt Extrusion*, 52 European J. of Pharmaceutics and Biopharmaceutics 181, 190 (2001) (DTX-141). Indeed, four other pieces of prior art disclose hot-melt-extrusion’s value in creating hard tablets. See (DTX-139), (DTX-137); (DTX-153); (DTX-164).

The court is persuaded that a person of ordinary skill in the art would understand that a thermoformed tablet containing PEO would be unusually hard. An unusually hard tablet is more difficult to crush than a softer tablet, and thus would reduce the potential for abuse by crushing. Thus, the prior art discloses “an abuse-proofed thermoformed dosage form as required by Claim 1 and the dependent claims of the ’060 Patent.

2. The McGinity Application Discloses Active Ingredients With Abuse Potential.

The McGinity Application also discloses active ingredients with abuse potential, including opioids. The invention calls for the mixture of PEO and a “therapeutic compound.” McGinity Application at 2:25–29. It defines “therapeutic compounds” to include a host of substances, including valium (diazepam). *Id.* at 8. As Dr. Davis conceded at trial, valium is known to be addictive. Trial Tr. at 2556:2–5.

McGinity also lists analgesics as suitable therapeutic compounds. McGinity Application at 8:20. In 2002, it was well understood that opioids are

analgesics. *See, e.g.*, Remington's Pharmaceutical Sciences 17 at 1103–05 (1985) (DTX-3201) (describing oxymorphone hydrochloride as one of several semisynthetic opiate analgesics); *see also* Goodman *et al.*, *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 491 (1985) (DTX-2781) ("The opioids are employed primarily as analgesics . . ."). A person of ordinary skill in the art, upon reading McGinity's disclosure of analgesics, would understand that analgesics include the known opioids, including oxycodone and oxymorphone. Thus, the McGinity Application discloses active ingredients with abuse potential, such as valium and opioids such as oxycodone and oxymorphone. Consequently, the McGinity Application discloses the relevant portions of Claim 1 of the '060 Patent ("one or more active ingredients with abuse potential"), and the relevant portions of claims 31 and 34 of the '060 Patent, which specify oxycodone and oxymorphone. *See* '060 Patent at 24:3–5; 13–15.

3. The McGinity Application Discloses the Polymer Limitations of the Asserted Claims.

The McGinity Application also discloses the various limitations of the asserted claims relating to the polymer used. McGinity discussed the use of high-molecular weight (1,000,000 – 10,000,000) PEO for use in hot melt extrusion, and actually tested numerous examples of tablets using such high-molecular weight PEO. *See* McGinity Application at 5:3–4; 19:11–34 (listing molecular weights of 1 million and 7 million). Thus, McGinity discloses the relevant limitations of claims 1, 4, and 30 of the '060 Patent, which require: (1) "at least one synthetic or natural polymer with a weight of at least 0.5 million;" that (4)

the polymer be selected from the “group consisting of polyethylene oxide;” and (30) that “the . . . polyethylene oxide have a molecular weight of from 1–15 million.” See ’060 Patent at 21:7–10, 19–24; 23:19–20. Because most of the McGinity’s tablets used PEO in proportions greater than 60% by weight, see McGinity Application at 19:15–33 (listing percentages of weight between 54% and 94%), it also discloses the substance of Claim 33 of the ’060 Patent. See ’060 Patent at 24:7–10 (“wherein the content of the polymer is at least 30% [corrected to 60%] by weight relative to the total weight of the dosage form.”). Finally, because McGinity provided that “the therapeutic compound may be . . . suspended in the polymer matrix of the formulation,” see McGinity Application at 8:6–7, it discloses the substance of Claim 24 of the ’060 Patent, which provides that the polymer “also serve[s] as a controlled release matrix material.” See ’060 Patent at 22:65–7.

4. The McGinity Application Discloses Breaking Strength in Excess of 500N.

While Dr. Muzzio’s recreation of the McGinity Application failed to inherently disclose abuse-proofing in the anticipation context (because he failed to use an ingredient with abuse potential), see *supra* Part B(2)(b), his tests succeeded in showing that McGinity inherently discloses breaking strengths above 500N. Indeed, Dr. Muzzio created hundreds of tablets according to the McGinity Application’s examples, and each of these tablets exhibited a breaking strength well above 2000N. See Muzzio Report at 34–36 (DTX-5119A). At trial, plaintiffs raised various criticisms of Dr. Muzzio’s methods, see, e.g., Trial Tr. at

2219 (noting that Dr. Muzzio had failed to record torque values), but the court finds these criticisms to be outweighed by the sheer breadth and thoroughness of his testing. Thus, the court is persuaded that the McGinity Application inherently discloses breaking strengths in excess of 500N as required Claim 1 of the '060 Patent. *See* '060 Patent at 21:12–13.

5. The Prior Art Discloses the Additional Barriers to Abuse Recited in Claim 9 of the '060 Patent.

Claim 9 of the '060 Patent recites six additional barriers to abuse to be incorporated into the dosage form. *See* '060 Patent at 21:37–51. These are: an irritant, a viscosity-increasing agent which forms a gel with the extract from the dosage form, an antagonist, an emetic (vomiting agent), a dye, and a bitter substance. *See* '060 Patent at 21:38–51. Each of these additional barriers to abuse is disclosed in the prior art.

Irritants were disclosed in a number of references, including a patent application filed in 2002 which described creating a dosage form incorporating an antagonist and “an irritant in an effective amount to impart an irritating sensation to an abuser upon administration of the dosage form after tampering.” *See* Abstract, United States Patent No. 7,332,182 (DTX-160). The reference expressly discloses the irritant capsaicin, the active ingredient in peppers. *Id.* at 6:59. The specification of the '060 Patent discusses the use of peppers and other “capsaicinoids” as irritants. *See* '060 Patent at 8:10. Thus, the court concludes that the prior art discloses the use of irritants described in Claim 9 part (a) of the '060 Patent.

The prior art also discloses the use of viscosity increasing agents. As discussed in the claim construction section of this opinion, a “viscosity increasing agent” is a substance, distinct from the hardening polymer, which increases the thickness of the dosage form extract by forming a gel when exposed to a liquid, such gel optionally remaining visually distinguishable. *See supra* Part(A)(1)(c)(iv). At trial, Dr. Muzzio explained that the McGinity Application discloses several substances that are known to be viscosity increasing agents, such as guar gum and alginic acid. Trial. Tr. at 2178:14–18; *see also* McGinity Application 13:27–30 (listing guar gum and alginic acid as “disintegrating agents”). This is important because Guar gum was later listed in the ’060 Patent as being a viscosity-increasing agent. ’060 Patent at 9:7. Thus, McGinity discloses distinct viscosity-increasing agents as required by Claim 9.

Antagonists, emetics, dyes, and bitter substances were well known in the art. The ’119, ’088, and ’182 patent applications, each filed before 2003, all describe the use of antagonists to deter abuse of prescription drugs. *See supra* Part (B)(2)(c)(i). Emetics, like the syrup of ipecac, were commercially available, as were dyes and bitter substances. *See* Trial Tr. at 1105-06.

The court is persuaded that each of the additional barriers to abuse recited in Claim 9 of the ’060 Patent were disclosed in the prior art. Moreover, once an artisan had set out to create an abuse-proofed tablet, it would have been obvious to integrate one or more of these additional barriers along with the feature of unusual hardness as required by the claim. *See* ’060 Patent at 21:37. Indeed, much of the prior art used a multiple-barrier approach, integrating two or more

features, such as the use of an antagonist and irritant, to prevent abuse. *See, e.g.,* '182 Patent at 2:67–33 (DTX-161

Thus, the court concludes that the prior art discloses the substance of Claim 9 of the '060 Patent. Likewise, claims 25, 26, and 27, which also incorporate additional barriers to abuse, were also disclosed. To the extent those claims recite “press-forming” and a “melt process” as additional limitation, those limitations were disclosed by the McGinity Application, which teaches “compression molding” and hot-melt extrusion. *See* McGinity Application at 11:–8.

The court concludes that each limitation of the asserted claims of the '060 Patent was disclosed in the prior art. The McGinity Application, while insufficient to anticipate the invention, nonetheless discloses many of its components. The remainder of the components were disclosed by other references.

iii. Whether Secondary Considerations Indicate the Non-Obviousness of the '060 Patent.

The final step in the obviousness analysis requires consideration of objective indicia of non-obviousness, such as the commercial success of the invention, the invention's satisfaction of a long-felt but unmet need, the failure of others to solve the problem at hand, and the copying of the invention by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

The commercial success of the invention indicates its non-obviousness. At trial, Dr. Alexander Kraus, explained that Grünenthal has successfully licensed its crush-resistance technology to branded-drug manufactures Johnson & Johnson, Purdue Pharma, and Endo, for use in their flagship opioid products.

Trial Tr. at 1380. The revenue from these licenses is significant. Revenues earned from reaching certain development milestones with these companies total 116 million euros. *Id.* at 1391. In addition, these companies have paid Grünenthal royalties totaling 312 million euros. *Id.* In all, Grünenthal has earned 428 million euros, or \$556 million, from licensing its crush-resistant technology to American branded-drug manufacturers. Trial Tr. at 1392:5–10. Thus, Grünenthal has enjoyed clear and indisputable commercial success for its product. This success is directly related to the asserted claims, because each of the license agreements involved developing abuse-deterrent dosage forms, and abuse-deterrence is the primary feature of the asserted claims of the '060 Patent. *See* Trial Tr. at 1385–88.

However, there does not appear to have been a long-felt need for the invention. Dr. Bartholomäus testified that Grünenthal began exploring abuse deterrence to confront the crisis of OxyContin abuse in the United States. Trial Tr. at 984:15–19. Dr. Lee testified that OxyContin only achieved widespread use “in the late '90's.” Trial Tr. at 236:5–7. And it didn't become widely abused until the early 2000's. *See* Trial Tr. at 2840:10–24. Thus, there was at most only a few years separating the rise of OxyContin abuse and Grünenthal's invention.

Moreover, Grünenthal's evidence of skepticism and industry acclaim is unpersuasive. As evidence of skepticism, Grünenthal's experts testified that the company was met with incredulity when it first set out to sell its technology. *See, e.g.,* Trial Tr. at 2542–43 (“[W]hen he [Bartholomäus] first began describing his invention, people were skeptical. His colleagues at Grünenthal were skeptical,

people from Purdue or from Endo who were interested in the technology were skeptical”). Members of the industry doubted that a tablet as hard as Grünenthal’s could actually release the active ingredient. *Id.* at 2543. Grünenthal offered similar “evidence” of industry acclaim. Trial Tr. at 2545. (“The potential licensees, when they visited Grünenthal and saw the technology and saw not just the hardness but the release data, were indeed impressed. And I think a couple of the people said this is the best technology we have seen so far to date.”). In the court’s view, this evidence is too anecdotal to be useful. Grünenthal failed to provide tangible evidence that its invention was met with anything more than passing incredulity, and its only evidence of industry acclaim is secondhand and underwhelming.

Conclusion Regarding the Validity of the ’060 Patent

Defendants have shown, by clear and convincing evidence, that the asserted claims of the ’060 Patent would have been obvious to a person of ordinary skill in the art at the time of the invention. The art in 2002 demonstrated a clear motivation to solve the problem of prescription opioid abuse, including abuse that requires, as a first step, the crushing and pulverization of the dosage form. The art surrounding the branded drug Concerta showed a motivation to make a tablet unusually hard as a means of deterring abuse through crushing and snorting.

In light of this motivation, a skilled artisan would have been led to the prior art teaching the hardness-conferring properties of both hot-melt extrusion and polyethylene oxide. This art included the McGinity Application, which

discloses the hot-melt extrusion of PEO with therapeutic compounds, a process identical, in all crucial respects, to thermoforming. The McGinity Application also discloses many of the '060 Patent's other salient features, including active ingredients with abuse potential, the relevant polymer limitations, and a breaking strength above 500N. These disclosures are supplemented by art describing all of the secondary barriers to abuse recited in Claim 9 of the '060 Patent.

The commercial success of the invention favors Grünenthal, but there was no significant showing of skepticism and acclaim. And even if all the secondary factors favored Grünenthal, the court would nonetheless rule in defendants' favor given their strong showing of obviousness over the prior art.

In the end, the court finds that Grünenthal's invention was obvious when made. Defendants have satisfied their burden and shown, by clear and convincing evidence, that the asserted claims of the '060 Patent are invalid.²¹

C. Roxane's Unclean Hands Defense.

Roxane Laboratories, Inc. asserts unclean hands as an equitable defense to Endo's claims. Roxane argues that Endo, in order to settle an earlier patent infringement case, agreed to not oppose Roxane's launch of its generic

²¹ Defendants also argue that the asserted claims of the '060 Patent are invalid for lack of enablement, lack of written description, and indefiniteness. The court disagrees. The patents would teach a skilled artisan how to practice the full scope of the invention without undue experimentation, and would also convey that Grünenthal possessed the entirety of the claimed invention. Thus, the claims are not invalid for lack of enablement and written description. Regarding indefiniteness, the court concludes that each of the asserted claims, including Claim 9 of the '060 Patent, is sufficiently defined to convey the metes and bounds of the invention. Thus, defendants' Section 112 arguments are without merit.

oxymorphone product after a certain date. Roxane claims that after the settlement of the earlier case was complete, Endo took a number of steps to perpetually stall the launch of its generic product. Roxane argues that these actions amount to inequitable conduct which preclude Endo from obtaining an injunction from this court.

The United States courts are courts of law and equity. U.S. Const. art. III § 2. As courts of equity, district courts are closed to those “tainted with inequitableness or bad faith relative to the matter” in which they seek relief. *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945). Otherwise, they would risk becoming “abettors of iniquity,” giving judicial sanction to those who have acted deceitfully and unfairly to gain an advantage. *See Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933).

In 2009, Roxane filed an abbreviated new drug application to sell a generic version of OPANA®ER. At the time, Endo had three patents in the Orange Book listed as covering the branded drug: the '933 Patent, the '456 Patent, and the '250 Patent. Endo sued Roxane for patent infringement (the “First Action”). However, the litigation was eventually settled pursuant to a Settlement and License Agreement. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Two years before Roxane and Endo settled the First Action, Roxane had entered into a supply agreement with Johnson Matthey Inc. (“JMI”) whereby JMI agreed to supply Roxane oxymorphone hydrochloride, the active ingredient in Roxane’s planned generic product. *See* Supply Agreement Sched. A (DTX-2221). After the Supply Agreement was executed, JMI was awarded a patent, Number 7,851,482, concerning a new, low toxicity formulation of oxymorphone hydrochloride (the “482 Patent”). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] JMI sold the '482 Patent to Endo pursuant to a Patent Purchase Agreement. See Patent Purchase Agreement (DTX-2209).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In 2012, Endo was awarded two new patents, the '122 and '216 patents, which cover its branded-oxymorphone product. In May of 2013, Endo filed the instant lawsuit against Roxane for patent infringement, asserting both its newly won patents (the '122 and '216 Patents) and the patent it had purchased from Johnson Matthey (the '482 Patent). See Compl. ¶¶ 18-25. As trial on these

patents approached, Endo stopped asserting the '482 Patent. Thus, only the '122 and '216 patents were litigated at trial. Endo has also filed a third lawsuit against Roxane in the District of Delaware, asserting infringement of another patent.

Having reviewed Endo and Roxane's evidence *in camera*, the court concludes that Endo has not acted inequitably in this case. Roxane's unclean hands defense is less complicated than it seems, and amounts to this: [REDACTED]

[REDACTED] but (2) after the settlement was finalized, Endo took a number of steps, [REDACTED] and filing two new lawsuits, in order to perpetually prevent Roxane from entering the market.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Finally, Endo stopped asserting the '482 Patent in this case. Thus, the court see no relationship between Endo and JMI's actions and the matters asserted at trial.

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Roxane, to challenge those patents. But generic manufacturers are sophisticated entities, and upon settling litigation regarding one patent are perfectly capable of insisting that the settlement cover future patent issuances. There is nothing inequitable about a company, like Endo, asserting wholly different patents when they issue or are otherwise acquired.

Conclusion

For the reasons given above, the court concludes that defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that defendants have failed to satisfy their burden of showing those claims to be invalid. The court concludes that defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid.

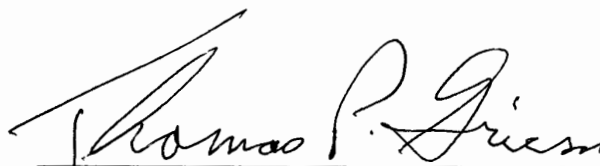
The court enters judgment in Endo's favor and enjoins defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents. Moreover, the court orders that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents. See 35 U.S.C. § 271(e)(4).

Because defendant Actavis is already on the market with its generic product, it shall have sixty days from the date of this decision to comply. The court reserves decision on whether to award additional relief, including damages against defendant Actavis, pending further briefing from the parties.

Endo's recently filed motion to strike Amneal's obviousness defense in case number 12-CV-8115 is moot. The clerk of court is directed to resolve all pending motions in the above captioned cases.

SO ORDERED.

Dated: New York, New York
August 14, 2015



Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,,

Plaintiffs,

-against-

AMNEAL PHARMACEUTICALS, LLC and
AMNEAL PHARMACEUTICALS OF NEW
YORK, LLC,

Defendants.

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,,

Plaintiffs,

-against-

TEVA PHARMACEUTICALS USA, INC. and
BARR LABORATORIES, INC.

Defendants.

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

-against-

IMPAX PHARMACEUTICALS, INC. and
THORX LABORATORIES, INC.,

Defendants.

-----X
ENDO PHARMACEUTICALS INC.,

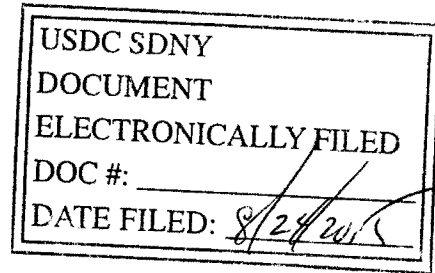
Plaintiff,

-against-

ACTAVIS INC. and ACTAVIS SOUTH
ATLANTIC LLC,

Defendants.

-----X



12 **CIVIL** 8115 (TPG)

JUDGMENT

12 **CIVIL** 8060 (TPG)

JUDGMENT

12 **CIVIL** 8317 (TPG)

JUDGMENT

12 **CIVIL** 8985 (TPG)

JUDGMENT

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiff,

13 **CIVIL** 435 (TPG)

-against-

JUDGMENT

IMPAX LABORATORIES, INC.,
Defendants.

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiff,

13 **CIVIL** 436 (TPG)

-against-

JUDGMENT

ACTAVIS INC, ACTAVIS SOUTH
ATLANTIC LLC, and WATSON
PHARMACEUTICALS INC.,
Defendants.

-----X
ENDO PHARMACEUTICALS INC.,

Plaintiff,

13 **CIVIL** 3288 (TPG)

-against-

JUDGMENT

ROXANE LABORATORIES INC.,
Defendant.

-----X
ENDO PHARMACEUTICALS INC.,

Plaintiff,

13 **CIVIL** 4343 (TPG)

13 **CIVIL** 8597 (TPG)

-against-

JUDGMENT

SUN PHARMACEUTICALS INDUSTRIES,
LTD.

Defendant.

-----X

Whereas the above-captioned action having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiffs Endo Pharmaceuticals Inc. (“Endo”) and Grünenthal GmbH (“Grünenthal”) argue that defendants, all of which are generic drug manufacturers, infringe on patents covering Endo’s branded painkiller OPANA®ER by selling or seeking approval to sell generic versions of the drug in either crushable or non-crushable formulations; Defendants argue that their generic products, as described in their abbreviated New Drug Application (“ANDAs”), do not and will not infringe the patents-in-suit, and that in any event those patents are invalid; Defendants also asserted other statutory and equitable defenses; there are seven groups of defendants in these cases; Plaintiff sued the defendants separately, but the case were tried jointly upon the mutual consent; the Defendants are: Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively, “Amneal”); Teva Pharmaceuticals USA, inc. and Barr Laboratories, Inc. (Collectively, “Teva”); Impax Laboratories, Inc. (“Impax”), ThoRx Laboratories, Inc. (“ThoRx”) Actavis South Atlantic LLC, and Watson Pharmaceuticals, Inc. (Collectively, “Actavis”); Roxane Laboratories, Inc. (“Roxane”) and Sun Pharmaceutical Industries (“Sun Pharma”); There are three patents-in-suit; Endo owns two of the patents, United States patent numbers 8,309,122 (“the ’122 Patent”) and 8,329,216 (“the ’216 Patent”)’ these parties recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; Grünenthal owns the third patent, United States Patent Number 8,309,060 (“the ’060 Patent”), which describes an invention for drug-tablets so hard that they are difficult to abuse through crushing and snorting, and which also accommodate other barriers to abuse, and the matter having come before the Honorable Thomas P. Griesa, United States District Judge, and the Court, on August 14, 2015, having rendered its Findings of Fact and Conclusion of Law the Court concluding that defendants’ generic products, as described in their ANDAs, infringe all but two of the asserted claims of the ’122 and ’216 patents, and that defendants having failed to satisfy their burden of showing those claims to be invalid; the Court concluding that defendants infringe the asserted claims of the ’06 Patent, but that they have satisfied their burden and shown those claims to be invalid; the Court enters judgment in favor of Endo’s favor and enjoining defendants from making or selling their generic products prior to the expiration of the ’122 and ’216 patents; moreover, the Court ordering that the effective date of approval of defendants’ ANDAs shall be no sooner than the expiration date of the ’122 and ’216 patents; because defendant Actavis

is already on the market with its generic product, it shall have sixty days from August 14, 2015, the date of the decision to comply; the Court reserves decision on whether to award additional relief, including damages against defendant Actavis, pending further briefing from the parties; Endo's recently filed motion to strike Amneal's obviousness defense in he casei number 12-CV-8115 is moot; directing the Clerk of Court to enter to resolve all pending motions in the above caption cases, it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, that defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that defendants have failed to satisfy their burden of showing those claims to be invalid; that defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid; judgment is hereby entered in Endo's favor and enjoins defendants from, making or selling their generic products prior to the expiration of the '122 and '216 patents; moreover, the Court orders that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents; because defendant Actavis is already on the market with its generic product, it shall have sixty days from August 14, 2015, the date of the decision to comply; the Court reserves decision on whether to award addition relief, including damages against defendant Actavis, pending further briefing from the parties; Endo's recently filed motion to strike Amneals obviousness defense in case number 12-CV-8115 is moot.

Dated: New York, New York

August 24, 2015

RUBY J. KRAJICK

Clerk of Court

BY: _____

Deputy Clerk

**THIS DOCUMENT WAS ENTERED
ON THE DOCKET ON _____**

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----- x
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

AMNEAL PHARMACEUTICALS, LLC and
AMNEAL PHARMACEUTICALS OF NEW
YORK, LLC

Defendants.
----- x

12 Civ. 8115 (TPG)

ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC. and
BARR LABORATORIES, INC.

Defendant.
----- x

12 Civ. 8060 (TPG)

ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

IMPAX LABORATORIES, INC. and THORX
LABORATORIES, INC.

Defendants.
----- x

(captions continued on
following pages)

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ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	
	:	12 Civ. 8985 (TPG)
ACTAVIS INC. and ACTAVIS SOUTH	:	
ATLANTIC LLC,	:	
	:	
Defendants.	:	
-----	X	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	13 Civ. 435 (TPG)
	:	
IMPAX LABORATORIES, INC.,	:	
	:	
Defendants.	:	
-----	X	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	13 Civ. 436 (TPG)
	:	
ACTAVIS INC, ACTAVIS SOUTH	:	
ATLANTIC LLC, and WATSON	:	
PHARMACEUTICALS, INC.,	:	
	:	
Defendants.	:	
-----	X	

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ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13 Civ. 3288 (TPG)
	:	
ROXANE LABORATORIES, INC.,	:	
	:	
Defendant.	:	
	:	
-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13 Civ. 4343 (TPG)
	:	13 Civ. 8597 (TPG)
SUN PHARMACEUTICAL INDUSTRIES,	:	
LTD.	:	
	:	
Defendant.	:	
-----	x	

Omnibus Opinion

Defendants Actavis, Inc. and Actavis South Atlantic LLC (together, “Actavis”) and Roxane Laboratories, Inc. (collectively, “Moving Defendants”) have filed motions under Federal Rules of Civil Procedure 52(b), 59(e), and 60(a) to alter, amend, or correct the judgment; motions and requests to strike and unseal; requests to alter the complaint per Rule 15(b); a request to stay this matter pending appeal; and a request to schedule a damages trial and order discovery relating to damages. Certain other defendants have filed similar motions. This flurry of filings followed a five-week, consolidated bench trial and a 154-page opinion of August 14, 2015 in which the court found, in relevant part, that the Moving Defendants infringed the ’122 and ’216 patents of Endo Pharmaceuticals, Inc.

For the following reasons, the court declines to alter the effective dates of Moving Defendants’ Abbreviated New Drug Applications (“ANDAs”) but exercises its equitable power to enjoin Moving Defendants. In addition, the court denies Actavis’s request for a stay and Endo’s request to schedule a damages trial and order discovery.

Background

Shortly after this court held, in relevant part, that Moving Defendants’ generic products infringed Endo’s ’122 and ’216 patents, *Endo Pharms, Inc. v. Roxane Labs., Inc.*, No. 13-cv-3288, ECF No. 194 at 55–58, 68 n.10, Moving Defendants filed separately to alter or amend the court’s judgment per Rule 59(e) or, in the alternative, for a stay pending appeal, *Endo Pharms. v. Actavis Inc.*, No.

12-cv-8985, ECF Nos. 109–12 (Actavis briefing); *Endo Pharms. v. Roxane Labs., Inc.*, No. 13-cv-3288, ECF Nos. 202–03 (Roxane briefing). Endo filed its own motions to amend and correct the judgment under Rules 52(b) and 60(a). *Endo Pharms. v. Teva Pharms. Inc.*, No 12-cv-8060, ECF No. 240; No. 12-cv-8985, ECF Nos. 113–15, 124. The parties then exchanged oppositions, replies, requests to strike, and, in Endo’s case with respect to Actavis’s Rule 59(e) motion, an unauthorized surreply under seal. On February 16, 2016, Actavis moved to strike Endo’s surreply and the declaration attached thereto, and to have those documents filed on the public docket. No. 12-cv-8985, ECF Nos. 150–51. These matters are now fully briefed before the court.

Discussion

A. Motions to Alter or Amend

The court will first consider Endo’s motion to alter or amend the judgment under Rule 52(b), No. 12-cv-8060, ECF Nos. 240–41, and Moving Defendants’ separate motions to alter or amend the judgment under Rule 59(e), No. 12-cv-8985, ECF Nos. 109–12 (Actavis briefing); No. 13-cv-3288, ECF Nos. 202–03 (Roxane briefing).

Rules 52(b) and 59(e) give the court discretion to alter or amend its findings and judgment. We review Rule 59(e) and Rule 52(b) motions under the same standard. *Soberman v. Groff Studios Corp.*, 2000 WL 1253211, at *1 n.1 (S.D.N.Y. Sept. 5, 2000). A district court may grant a Rule 52(b) or Rule 59(e) motion to correct manifest errors of law or fact at trial, *Muyet v. United States*, No. 01-cv-9371, 2005 WL 1337369, at *2 (S.D.N.Y. June 6, 2005) (citation

omitted), or, in some limited situations, in the face of newly discovered evidence. *Bazuaye v. United States*, No. 09-cv-8288, 2011 WL 1201696, at *1 (S.D.N.Y. 2011) (citation omitted).

Despite their similarities, Rule 52(b) and Rule 59(e) motions have distinct applications. Rule 52(b) provides a method to dispute underlying facts that resulted in faulty factual findings or conclusions of law based on those facts. Rule 59(e) provides for a broad request for reconsideration of the judgment itself. Under Rule 59(e), this court may alter or amend the judgment only “to correct a clear error of law or prevent manifest injustice.” *Schwartz v. Liberty Mut. Ins. Co.*, 539 F.3d 135, 153 (2d Cir. 2008) (citation omitted). Where a party fails to dispute facts in the record, a motion under Rule 52(b) is inappropriate. *Muyet*, No. 01-cv-9371, 2005 WL 1337369, at *2.

Endo’s arguments in its Rule 52(b) motion are legal in nature. It asks the court to address the Supreme Court’s decision in *eBay, Inc. v. MercExchange, LLC*, 547 U.S. 388 (2006). And although Endo’s Rule 52(b) motion appends proposed additional findings of fact in addition to conclusions of law for the court to consider, those facts are all in service of a purely legal finding under *eBay*. Thus, Endo’s September 21, 2015 motion must be construed as a motion under Rule 59(e). *See United States v. Local 1804-1, Int’l Longshoremen’s Ass’n*, 831 F. Supp. 167, 169 (S.D.N.Y. 1993) (holding that a Rule 52(b) motion is an inappropriate way to advance new legal theories, relitigate old issues, or rehear judgments on the merits).

Here, the two core issues to be decided under Rule 59(e) are: (1) whether the effective date of Moving Defendants' ANDAs should be altered, per 35 U.S.C. § 271(e)(4)(A); and (2) whether the court should issue an injunction against Moving Defendants. For the reasons set forth in detail below, the court will alter and amend its order and judgment as to both issues.

a. *Remedies Under 35 U.S.C. § 271(e)(4)(A)*

Before the court directly addresses the Rule 59(e) motions, the court will first give greater context to the § 271 statutory scheme and to the pharmaceutical patent process, more generally.

When a drug pioneer creates and sufficiently tests a new product, the pioneer submits a New Drug Application ("NDA") to the U.S. Food and Drug Administration ("FDA"). A patent for that new drug can issue before or after the FDA approves the NDA. Once the FDA approves an NDA, however, the pioneer enjoys a period of regulatory exclusivity.

The Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act created § 505(j) (codified at 21 U.S.C. § 355(j)), which established the ANDA-approval process. That process permits generic versions of previously-approved innovator drugs to be approved without submission of a full NDA. The ANDA process can save drug companies time and money because it allows the ANDA to refer to a previously approved NDA and to rely upon the FDA's finding of safety and effectiveness for that drug product.

While Congress made it easier for generic drug companies to access the market through the ANDA process, Congress also imposed limitations on generic

companies. For certain types of drugs, Hatch-Waxman established a period of marketing exclusivity during which time generic drug companies cannot submit an ANDA. See 21 U.S.C. § 355(j)(5)(F). As a mechanism of enforcement before the generic drug company begins marketing its product, Congress enabled patent holders of pioneer drugs to establish in court that there has been an act of infringement. See 35 U.S.C. § 271(e)(2); see also *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 668 (1990) (explaining that the Hatch-Waxman “scheme will not work, of course, if the holder of the patent pertaining to the pioneer drug is disabled from establishing in court that there has been an act of infringement”).

Section 271(e)(2)(A) thus makes it “an act of infringement to submit an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]” If a fact-finder has found that a defendant has infringed a patent under 35 U.S.C. § 271(e)(2), the statute provides that “the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed.” § 271(e)(4)(A). The court may also grant additional remedies, including a permanent injunction or the award of monetary damages. § 271(e)(4)(B)–(C).

In motions before this court, Actavis argues that the effective dates of its ANDAs should not have been changed under § 271(e)(4)(A), and Roxane seeks alteration or amendment of the judgment to reflect that it did not infringe the ’122 and ’216 patents under § 271(e)(2). The court addresses these requests in

tandem because they ask essentially the same question: whether Moving defendants infringed the '122 and '216 patents under § 271(e)(2) such that Endo is entitled to relief under § 271(e)(4)(A).¹

The statutory scheme created by the Hatch-Waxman Act and § 271(e)(2) does not permit Endo to obtain relief against Moving Defendants under § 271(e)(4)(A). This is so because the '122 and '216 patents had not issued at the time Moving Defendants filed their ANDAs. As alluded to above, § 271(e)(2)(A) provides a patentee with a cause of action for patent infringement based solely upon the filing of an ANDA containing a certification implicating a patentee's rights. And as noted above, § 271(e)(2) makes it an act of infringement to submit an ANDA under § 355(j) for "a drug claimed in a patent or the use of which is claimed in a patent." Notably, the subject of the sentence is "a patent," not a provisional patent application or a patent-pending. Moreover, the statute's use of the past-tense phrase "claimed in a patent" suggests that the ANDA must relate to a drug that has *already* been claimed in a patent. In other words, the statute requires the prospective ANDA to relate to a patent that had already been issued at the time of the ANDA's submission. *Accord Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc.*, 821 F. Supp. 2d 681, 697 (D. N.J. 2011), *aff'd sub nom. Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354 (Fed. Cir. 2014) (finding that infringement under 35 U.S.C. § 271(a)-(c) does not trigger § 271(e)(4)).

¹ As the parties should be aware, the court's analysis here applies only to those ANDAs submitted by Moving Defendants prior to the issue of Endo's patents.

The Federal Circuit's decision in *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366 (Fed. Cir. 2006), is not to the contrary. In that case, Impax submitted an ANDA based on a patent that had issued years before. However, Impax received FDA approval of its ANDA before any relevant patent was listed in the public listing of patents, often referred to as the Orange Book. *Id.* at 1372–73. Impax became aware of a relevant patent while preparing its ANDA. *Id.* A dispute arose between Impax and the prospective patent-holder, and, before trial, Impax and the patentee ultimately entered into a stipulation whereby Impax conceded that its ANDA product infringed various claims of the patentee's patent. *Id.* The parties proceeded to litigate and try the case on other grounds. Going forward, however, neither the district court nor the Federal Circuit actually addressed whether an infringement action under § 271(e)(2) can lie where a patent was issued after the filing or approval of an ANDA. It is therefore improper to cite *Impax* for the proposition that a patent-holder can maintain an action under § 271(e)(2) where the patent issued after the filing of an ANDA.

Endo's argument in opposition would impose infringement liability on an ANDA filer if a patent were to issue *at any time* after the ANDA is filed. This argument has no basis in the text and it overlooks a primary purpose of the Hatch-Waxman Act, which is to facilitate “the early resolution of patent disputes between generic and pioneering drug companies by providing that the mere act of filing . . . [an] ANDA constitutes an act of patent infringement.” *Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1283 (Fed. Cir. 2008) (citing 35 U.S.C. § 271(e)(2)). The statute allows a court to find an existing case or

controversy even though the generic drug has not yet been marketed or sold. *Id.* at 1283–85. Congress’s creation of this early-stage cause of action is what makes a suit under § 271(e)(2) “artificial.” See *Eli Lilly*, 496 U.S. at 678. But this early-stage adjudication is useless if, at the time the generic drug company submits its ANDA, no patent has issued.

The proposed statutory scheme would also delay or even prevent ANDA-filers from enjoying finality with respect to litigation risk. Downstream holders of partial patents could sue ANDA-filers, even though those downstream partial patent holders were never conceived of at the time that the generic company submitted its ANDA. This uncertainty conflicts with other purposes of the statute, which include “facilitat[ing] the development of generic versions of listed drugs,” *Caraco*, 527 F.3d at 1282, and “incentiviz[ing] ANDA filers to challenge the validity of listed patents or design around those patents as early as possible,” *id.*

Ultimately, there is no textual support for the notion that the statute was drafted to provide post-ANDA patent holders with a “gotcha” cause of action based on the filing of the ANDA when the patent issues years after. Rather, the simplest and most cogent interpretation holds that it is an act of infringement to submit an ANDA for a drug claimed in a patent or the use of which is claimed in a patent *when that patent is issued at the time a company submits its ANDA*.

The ’122 and ’216 patents issued years after Moving Defendants filed the relevant ANDAs. Accordingly, Endo cannot be awarded relief under § 271(e)(4)(A)

because it was not eligible for infringement liability under § 271(e)(2).² The court's findings of fact and law as well as the judgement will be amended and altered accordingly.³

b. *Injunctive Relief*

While the court has found that Endo is not eligible for the relief set forth in § 271(e)(4), the court has the general equitable power to issue an injunction upon the finding of patent infringement under § 271(a)–(c). *See, e.g., eBay*, 547 U.S. 388.

Before the court can enjoin Moving Defendants, Endo must demonstrate that such relief would be fair and equitable pursuant to the Supreme Court's analysis in *eBay*. In that case, the Court recognized that a patent owner prevailing on the merits in a patent infringement suit is not automatically entitled to an injunction. *eBay*, 547 U.S. at 390. Rather, courts apply traditional equitable principles to determine: (1) whether the patentee would be irreparably harmed without an injunction; (2) whether the patentee has an adequate remedy at law; (3) whether the balance of hardships favors an injunction; and (4) whether granting the injunction is in the public interest. *Id.* at 391. The court will apply these considerations to the facts of this case.

² For this reason, requests to alter the complaint per Federal Rule of Civil Procedure 15(b) are denied.

³ It should be noted that this does not alter the court's original holding that relief under 35 U.S.C. § 271(e) is appropriate as to all defendants other than Roxane and Actavis. Those other defendants were found to infringe under § 271(e)(2)(A) and thus the court alters the effective dates of the relevant ANDAs, in compliance with § 271(e)(4)(A). The court will determine whether an injunction is appropriate under § 271(e)(4)(B) after considering the parties' briefing on the issue. *See infra* n.4.

i. Irreparable Harm

A patentee must show that it would suffer irreparable harm from infringement if the court were to decline to issue an injunction against the patent infringer. This requires proof that a “causal nexus relates the alleged harm to the alleged infringement.” *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012). The purpose of the causal nexus requirement is to establish the link between the infringement and the harm, to ensure that there is “some connection” between the harm alleged and the infringing acts. *Apple, Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1364 (Fed. Cir. 2013). Thus, a plaintiff can demonstrate irreparable harm “by showing that it will likely suffer an injury and, separately, satisfy the nexus requirement by showing that this injury is causally linked to the infringement.” *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 652 (Fed. Cir. 2015).

Where a plaintiff and an infringer directly compete in the same market, an injunction may be warranted to protect the plaintiff from irreparable harm. See *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013); see also Douglas Ellis et al., *The Economic Implications (and Uncertainties) of Obtaining Permanent Injunctive Relief After Ebay v. MercExchange*, 17 Fed. Circuit B.J. 437, 442 & nn.39–40 (2008). Competition is logically tied to injury, since directly competitive companies are most likely to be rivals for market share, sales, customers, profits, business opportunities, goodwill, and brand power.

When a patentee alleges it suffered irreparable harm stemming from lost sales solely due to a competitor’s infringement, a finding that the competitor’s

infringing features drive consumer demand for its products satisfies the causal nexus inquiry. *Id.* at 641. But this rule is neither categorical nor is it mechanically applied; the four-factor *eBay* analysis exists because it may well be impossible if for the patentee to proffer affirmative evidence showing direct causation. *See id.* Whether a patentee has made a causal showing is, of course, a discretionary determination. *Id.*

While injunctive relief is designed to address future harms, past harm is relevant as an indicator of the future. *Id.* at 652 (citing *United States v. Oregon State Med. Soc.*, 343 U.S. 326, 333 (1952) (Jackson, J.)). Accordingly, a patentee may rely on past irreparable harm as well as prospective harm to support its request for an injunction. *See eBay*, 547 U.S. at 391 (noting that a patentee must demonstrate that “it *has suffered* an irreparable injury”) (emphasis added); *see also i4i Ltd. P’ship v. Microsoft Corp.*, 598 F.3d 831, 861–62 (Fed. Cir. 2010) (finding that evidence of past irreparable harm was sufficient to support an injunction and citing cases); *Polymer Techs., Inc. v. Bridwell*, 103 F.3d 970, 975 (Fed. Cir. 1996) (discussing the relevance of past harm where the danger of future infringement exists).

A patentee’s willingness to license does not necessarily evince a lack of irreparable harm or preclude an injunction, *MercExchange, LLC v. eBay, Inc.*, 401 F.3d 1323, 1339 (Fed. Cir. 2005), *vacated and remanded on other grounds*, 547 U.S. 388 (2006), nor does the existence of other competitors in the market, *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1381 (Fed. Cir. 2005).

In this case, Endo, Roxane, and Actavis are direct competitors in the oxymorphone market. No. 12-cv-8985, ECF No. 121 at 12–16. The fact that Endo’s non-crushable tablet is not automatically substituted at the pharmacy for Moving Defendants’ crushable generics does not militate a different conclusion. It is not as if the formula of Endo’s tablet is “but a small component” of the tablet that Actavis seeks to continue producing. *See eBay*, 547 U.S. at 396–97 (Kennedy, J. concurring). Rather, the court found that Moving Defendants’ entire products infringed on Endo’s entire product. This infringement is not vitiated simply because the drugs differ in crush resistance.

Endo convincingly argued at trial that to allow additional generics, such as Roxane’s, into the market would cause injury to Endo. *See* Trial Tr. 854:22, 859:24–860:2, 888:21–889:1. In addition, Endo persuasively reasoned that Actavis’s presence in the market has caused and will continue to cause Endo to lose market share, profits, and goodwill. No. 12-cv-8985, ECF No. 121 at 19–22. And contrary to Actavis’s view that Endo would be harmed only by *additional* generics entering the market, Endo has provided and specifically described the harms that the sale of Actavis’s product has caused and would continue to cause. *Id.* It has substantiated those claims by citing to sales and market data, and has identified the market share, revenue, and customers that Endo has lost to Actavis. Specifically, Endo has lost eleven percent of its market share to Actavis, alone. *Id.* at 19. It was also forced to cut its pain sales force by one quarter, to reduce its promotional expenses, and to alter its research and development strategies. *Id.* at 20–22.

Endo's stated harms are no less valid simply because some are past harms. Actavis launched its infringing product "at-risk" in the face of a potential injunction after trial. The at-risk launch has already encroached on Endo's bottom line. In this way, the at-risk launch portends more harm to Endo if the court declines to grant Endo an injunction. The court finds that those harms are more than financial, but are reputational, organizational, and administrative. These intangible harms are irreparable, and there is also no reason to believe that Moving Defendants will stop infringing, or that the irreparable harms resulting from its infringement will otherwise cease, absent an injunction. See *Reebok Int'l, Ltd. v. J. Baker, Inc.*, 32 F.3d 1552, 1557 (Fed. Cir. 1994) (recognizing that "future infringement . . . may have market effects never fully compensable in money"); *Telequip Corp. v. Change Exch.*, No. 01-cv-1748, 2006 WL 2385425, at *2 (N.D.N.Y. Aug. 15, 2006).

Endo's past license to Impax pursuant to a litigation settlement does not negate the harms Endo has experienced and would suffer in the future from Moving Defendants' infringement. Endo's actual and potential losses of revenue, market share, and customers to Moving Defendants pose a true threat and require legal redress by this court.

ii. Adequacy of Legal Remedy

Certain competitive harms can be offset by money damages or other remedies at law. In this way, the first two *eBay* elements are closely tied. Yet legal remedies may not be able to adequately compensate for harms that are difficult to quantify. *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336,

1344 (Fed. Cir. 2013) (“Irreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion of reputation and brand distinction.”).

Endo has demonstrated that it has suffered and would continue to suffer difficult-to-quantify harms resulting from Moving Defendants’ infringement. The infringement has caused Endo to lose forty percent of its share of the oxymorphone market, Trial Tr. 819, eleven percent of which is directly attributable to Actavis alone, Lortie Decl. ¶ 8. These losses have compounded problems in ways that would be difficult to quantify. Namely, Endo claims that it has had to lay off twenty-five percent of its relevant sales force. Trial Tr. 826–27; DTX-2501 ¶¶ 16, 42–52; Lortie Decl. ¶¶ 6, 11–14. These layoffs may damage Endo’s reputation in its market segment and have also made the company less attractive to potential new hires. Trial Tr. 847–48, 853–54; DTX-2501 ¶¶ 42–52; Lortie Decl. ¶¶ 11–14. Endo’s decline has caused it to decelerate its investment in research and development. Trial Tr. 857–59; Lortie Decl. ¶¶ 11–14. These are precisely the types of irreparable harm that an injunction is designed to remedy. Simple remuneration would not adequately address these irreparable harms.

iii. Balance of Hardships

Endo has argued that it will suffer hardship if the court does not enjoin Moving Defendants from infringing Endo’s patent. With respect to Actavis, Endo preemptively argues that any of Actavis’s purported harms are of its own making when it launched at-risk. No. 12-cv-8985, ECF No. 121 at 22–23. Actavis, on

the other hand, has not argued that it would suffer hardship. Rather, Actavis expounds on the ways in which *Endo* has supposedly failed to show hardship. *See id.* ECF No. 111 at 4–12. Actavis also asserts that “there is no evidence that enjoining Actavis’s product will materially benefit . . . Endo.” *Id.* at 11. These assertions are not the same as a supported statement that Actavis would suffer hardship. The court’s task is to weigh one party’s potential hardship against the other’s, and Actavis’s silence as to its own hardship is significant.

Roxane’s reasoning suffers from a similar defect. Roxane makes no affirmative arguments as to why Endo does not deserve an injunction. Rather, it argues incorrectly that Endo cannot be awarded an injunction if it neither pled nor won its infringement suit on § 271(e)(2) grounds. No. 13-cv-3288, ECF No. 202, at 2–3; No. 13-cv-3288, ECF No. 216, at 1–3. In addition, Roxane has not described the hardship it would suffer in the event the court enjoined its future infringement of the ’122 and ’216 patents.

The court has found above that Endo would suffer irreparable harm from Moving Defendants’ continued infringement. The scale tips in favor of Endo where Moving Defendants have not shown that they would suffer hardship.

iv. Public Interest

The court likewise finds that “the public interest would not be disserved by a permanent injunction.” *eBay*, 547 U.S. at 391. Endo is the rightful patent owner, and the Federal Circuit “has long acknowledged the importance of the patent system in encouraging innovation. Indeed, the ‘encouragement of investment-based risk is the fundamental purpose of the patent grant, and is

based directly on the right to exclude.” *SanofiSynthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006) (quoting *Patlex Corp. v. Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir. 1985)).

Endo has also provided sound reasons why the public interest would affirmatively favor an injunction. Crushable tablets, like the ones marketed by Moving Defendants, are more easily abused by patients. To the extent that the injunction also serves the interest of making a heavily-abused opioid less susceptible to abuse, the public interest is served. *See* PTX-937 (opining that reducing availability of “non-tamper-resistant” opioids serves the public interest); Trial Tr. at 830, 845, 2807. It should also be noted that there is also a public interest in protecting and promoting patent rights. *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005). The public interest factor weighs in favor of enjoining Moving Defendants.

In sum, all four *eBay* factors support enjoining Moving Defendants with respect to the infringing claims on the ’122 and ’216 patents.

B. Motion to Stay

The court has found that the *eBay* factors favor granting an injunction against Moving Defendants. Yet Actavis seeks a stay of this injunction pending appeal. No. 12-cv-8985, ECF No. 111 at 16. In deciding whether to suspend its injunction pending appeal, this court must consider: “(1) whether [Actavis] has made a strong showing that it is likely to succeed on the merits; (2) whether [Actavis] will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure [Endo]; and (4) where the public interest lies.”

Standard Havens Prods. v. Gencor Indus., 897 F.2d 511, 513 (Fed. Cir. 1990) (quoting *Hilton v. Braunskill*, 481 U.S. 770, 776 (1987)); *see also United States v. Eastern Airlines, Inc.*, 923 F.2d 241, 244 (2d Cir. 1991). When assessing those factors, the court follows a flexible approach and will require a lesser showing of harm if Actavis is likely to succeed on the merits on appeal and will require a more substantial showing of harm if the likelihood of success is low. *See Standard Havens*, 897 F.2d at 513–15. Considering the facts in this action in light of the standard set forth above, this court concludes that a stay is not warranted.

As to the first factor, Actavis tepidly states that on appeal it is likely to succeed or has “at least” a “substantial case.” No. 12-cv-8985, ECF No. 111 at 16. The only reason Actavis provides for this assertion is based on the court’s failure to recite the *eBay* factors in its August opinion. *Id.* The court has now applied the *eBay* factors, and those factors weigh against Actavis. Actavis offers no other substantial reasons as to this first factor.

On the second factor, Actavis argues that it would suffer irreparable harm absent a stay of the injunction. The stay would supposedly harm its goodwill and reputation in the industry because customers will be forced to undergo the difficult process of changing suppliers. *Id.* at 17–18. But these were the hazards Actavis accepted when it launched at-risk. It knew there was a patent infringement action against it and thus knew or should have known that there was a possibility—however remote—that it may someday be barred from

marketing the product in question. Actavis's anticipated harms are, thus, of its own making.

As to the third factor, Actavis next argues that Endo would not be harmed by such a stay. *Id.* at 18. But Endo convincingly argued that it has and would continue to suffer irreparable injury absent an injunction. The court agrees with that argument, and it equally agrees that a stay of the injunction would impose on Endo many of the same harms that a blanket injunction denial would. Moreover, recent product development by Endo indicates that Endo would particularly benefit from finality of this action and from the injunction at this time. Endo wishes to reinvigorate its marketing and development of Opana® ER and has taken steps to do so. No. 13-cv-8987, ECF No. 147. Delaying Endo its due remedy would impose further harm on it.

Finally, Actavis contends that the public interest favors a stay pending appeal because the first three factors above weigh in its favor. No. 12-cv-8985, ECF No. 111 at 18. With this circular reasoning, the court disagrees. While it is true that an injunction is a drastic remedy, an injunction can serve the ends of justice where it is warranted. The court holds that an injunction is warranted without a stay, whole or partial.

C. Motion to Correct

Endo has also moved to correct the judgment per Rule 60(a), which allows a court to "correct a clerical mistake or a mistake arising from oversight or omission whenever one is found in a judgment, order, or other part of the record." No. 12-cv-8985, ECF Nos. 113–15; Fed. R. Civ. P. 60(a). Rule 60(a) further

provides that, “after an appeal has been docketed in the appellate court and while it is pending, such a mistake may be corrected only with the appellate court’s leave.” This matter was appealed to the Federal Circuit but the Federal Circuit deactivated those appeals on November 10, 2015. *See Endo Pharms. Inc. v. Actavis Inc.*, No. 16-1025 (Fed. Cir. Nov. 10, 2015). Therefore, no appeals are currently pending and this court need not seek leave of the Federal Circuit to correct clerical mistakes under Rule 60(a).

Endo’s motion is opposed by Actavis, which is joined in opposition by defendants Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc. *See Endo Pharms. Inc. v. Actavis Inc.*, No. 13-cv-436, ECF No. 155 (Actavis’s opposition); No. 12-cv-8060, ECF No. 239 (Teva and Barr’s memorandum). The opposition argues that Endo’s requested amendments are outside the scope of Rule 60(b) because they are unnecessary and because the existing language is already clear. The court has found that certain of Endo’s corrections are well taken because they help to clarify the court’s intent at the time of issuing the judgment and do not rely on new evidence or reasoning. Accordingly, undisputed clerical errors and certain disputed amendments under Rule 60(b) will be made in a judgment to be docketed under a separate ECF number.⁴

⁴ Aside from Moving Defendants, the parties have not weighed in on how the four *eBay* factors favor or disfavor the imposition of an injunction in each particular case. The court will issue a separate Order inviting all parties aside from Moving Defendants to submit briefing on this topic. The final amended judgment in this case will be issued after that briefing is complete.

D. Motions & Requests to Strike

The court will now turn to the parties' various motions and requests to strike.

a. *Actavis's Motion to Strike Endo's Surreply & the Harlow Declaration*

Actavis has moved to strike as untimely and unseal Endo's surreply and the related Harlow declaration, No. 12-cv-8985, ECF No. 149, which respond in further opposition to Actavis's Rule 59(e) motion to alter or amend the judgment, No. 12-cv-8985, ECF Nos. 109–12. The court will strike the surreply as untimely and to remove it from seal.

It is beyond dispute that the decision to permit a litigant to submit a surreply is a matter left to the court's discretion, *Kapiti v. Kelly*, No. 07-cv-3782, 2008 WL 754686, at *1 n.1 (S.D.N.Y. Mar. 12, 2008), as is the decision to strike a party's filing, *Aurora Loan Servs., Inc., v. Posner, Posner & Assocs., P.C.*, 513 F. Supp. 2d 18, 19 (S.D.N.Y. 2007). Here, Endo neither sought nor received permission from the court to file a surreply to Actavis's motion to alter or amend the judgment. This contravenes the general principle that supplementary filings require leave of the court. Moreover, the filing ignores this court's individual rules, which specifically require leave to be sought if a party wishes to be heard outside the ordinary course. Individual Practices of Judge Thomas P. Griesa 2(C) (updated Nov. 18, 2014). Accordingly, this court exercises its discretion to grant Actavis's motion to strike Endo's unauthorized surreply and the Harlow declaration.

Actavis also asks the court to unseal Endo's now-stricken filing. Generally, there is a presumption that the public should be able to access all documents filed in this court. *SEC v. TheStreet.com*, 273 F.3d 222, 231 (2d Cir. 2001). Federal Rule of Civil Procedure 26(c) affords the court some discretion to decide whether and to what extent this general rule applies. In particular, a court may issue an order "requiring that a trade secret or other confidential research, development, or commercial information . . . be revealed only in a specified way." Fed. R. Civ. P. 26(c)(1)(g). This court did precisely that when it entered a protective order that permitted the parties to file certain papers under seal consistent with this court's individual rules. No. 12-cv-8985, ECF No. 31 at 1-2. That order requires parties seeking to file materials under seal to "move for permission to file the materials under seal contemporaneously." Individual Practices of Judge Thomas P. Griesa 3(B) (last updated Jan. 16, 2016). In such a motion, the party seeking protection bears the burden of establishing good cause for the issuance and continuation of a protective order. *Gambale v. Deutsche Bank AG*, 377 F.3d 133, 142 (2d Cir. 2004). In assessing whether good cause exists, courts in the Second Circuit look to whether the documents sought to be sealed are judicial documents to which the public has a presumptive right of access, the weight of that presumption, and the balance of competing considerations against that presumption. *Lugosch v. Pyramid Co. of Onondaga*, 435 F.3d 110, 119 (2d Cir. 2006); *see also United States v. Amodeo*, 71 F.3d 1044, 1048-52 (2d Cir. 1995).

In this matter, Endo has not provided specific information as to why its filings must be sealed. Rather, Endo stated flatly and without substantive explanation that the material discussed in its brief was “simply confidential.” No. 12-cv-8985, ECF No. 153 at 4. “But implicit in the notion of ‘confidential business information’ is something beyond the mere fact that the particular datum has not previously been made available to the public.” *Salomon Smith Barney, Inc. v. HBO & Co.*, No. 98-cv-8721, 2001 WL 225040, at *3 (S.D.N.Y. Mar. 7, 2001). Endo has fallen short of making the required showing to keep its materials confidential.

Even if Endo’s brief indeed contains confidential information meriting seal, Endo has not explained why it failed to seek permission to file under seal, nor has it justified why it declined to undertake the less restrictive approach of redacting the confidential parts of its brief and declaration. Accordingly, Endo may seek leave to redact confidential parts of its brief and declaration within ten days of the filing of this opinion. If no such request is made within ten days, the Clerk of Court is ordered unseal the brief and declaration and file them on the public docket.

b. *The Lortie Declaration*

Actavis contends that Endo improperly submitted the declaration of Brian Lortie, who previously submitted a declaration in support of Endo’s preliminary injunction motion in 2013 and who also testified before this court in the 2015 trial. No. 12-cv-8985, ECF No. 126, at 2–3. Lortie’s new declaration

accompanies Endo's opposition to Actavis's Rule 59(e) motion to alter or amend the judgment. No. 12-cv-8985, ECF Nos. 109–11.

Actavis argues that Lortie's new declaration is improper because it constitutes new evidence that Endo failed to offer at trial. In its defense, Endo simply asserts in a footnote that Lortie's declaration responds to Actavis's submission of the declaration of Andrew S. Boyer, No. 12-cv-8985, ECF No. 121 at 13 n.4, though Endo admits that Boyer's declaration is "principally directed" toward opposing Actavis's request for a stay of the injunction pending appeal. Endo adds that courts "frequently rely on" declarations accompanying post-trial motions.

However procedurally irregular the addition of the Lortie declaration may be, Actavis has not moved to strike it. Therefore, with respect to the Lortie declaration, there is no pending application or request for the court to decide. Therefore, the court has considered Lortie's declaration, particularly those parts that are corroborated by evidence and testimony given at trial.

It is also worth noting that Actavis has not argued that it has been deprived of a meaningful opportunity to respond to Endo's new post-trial declaration, nor has Actavis asked the court for leave to further brief any new evidence Lortie raises in his declaration.

c. Roxane's Request to Strike Endo's Opposition as Untimely

Roxane has asked the court to strike as untimely Endo's opposition to Roxane's Rule 59(e) motion. *Endo Pharms. Inc. v. Roxane Labs., Inc.*, No. 13-cv-3288, ECF No. 216 at 6. Endo countered by letter stating that its motion was

timely because its electronically-filed motion was entitled to a three-day extension. Letter from Brian M. Goldberg, Oct. 6, 2015, No. 13-cv-3288, ECF No. 218. Given this three-day allowance, for which Roxane neglected to account, Endo's opposition was timely. Roxane's request to strike Endo's opposition as untimely is denied.

d. *Timeliness of Endo's Rule 52(b) Motion*

Endo made a motion to alter or amend this court's findings and conclusions under Federal Rule of Civil Procedure 52(b), and Actavis has requested that the court strike this motion as untimely. No. 12-cv-8985, ECF No. 134, at 3-7. Rule 52(b) provides that, within 28 days after the entry of judgment, a party may ask the court to amend its findings and make additional findings, and the court may amend its judgment accordingly. A "judgment" is distinguishable from other pronouncements of the court, and the Rules specify that "[e]very judgment must be set out in a separate document." Fed. R. Civ. P. 58. The separate document rule is designed to reduce uncertainty for the litigants with respect to the date of final disposition of a case. *Axel Johnson Inc. v. Arthur Andersen & Co.*, 6 F.3d 78, 84 (2d Cir. 1993). The court entered judgment in this matter on August 24, 2016. Endo therefore had until September 21, 2016, to file a Rule 52(b) motion, and indeed Endo filed its motion on that day. The motion was timely.

E. Request for Damages Trial & Discovery

Endo also requests that this court schedule a damages trial and order Actavis to respond to certain outstanding discovery demands. The court declines

to do so at this time. Endo already consented to bifurcate liability from damages issues in this case. Appeals from this court's decision on liability will inevitably follow, and any decision from the Federal Circuit will surely affect the damages phase of this case. It is prudent to await the resolution of any appeal before scheduling a damages trial or conducting discovery related to damages. See *generally* 28 U.S.C. § 1292(c)(2) (providing that an appeal may be taken from a determination of liability without the district court being required to adjudicate damages); *Robert Bosch, LLC v. Pylon Mfg. Corp.*, 719 F.3d 1305 (Fed. Cir. 2013) (same). Endo's request is denied.

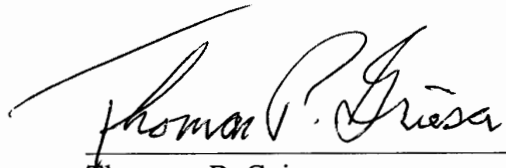
Conclusions

For the reasons set forth above, the court declines to alter the effective dates of Moving Defendants' ANDAs under 35 U.S.C. § 271(e)(4)(A) but enjoins Moving Defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents. The court declines to enter a stay pending appeal and declines to schedule a damages trial. Finally, the court will file a corrected judgment under a separate docket number.

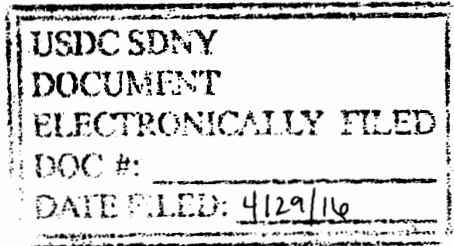
This omnibus opinion resolves all open items for the following docket numbers: 12-cv-8060, 12-cv-8115, 12-cv-8317, 12-cv-8985, 13-cv-0435, 13-cv-0436, 13-cv-3288, 13-cv-4343, and 13-cv-8597.

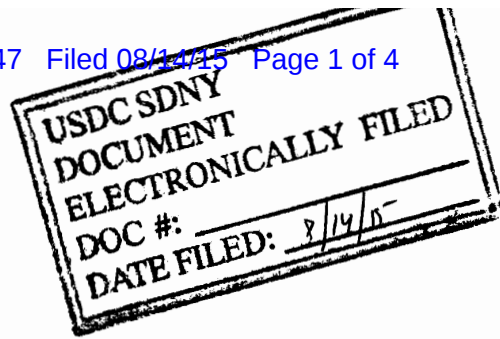
SO ORDERED.

Dated: New York, New York
April 29, 2016



Thomas P. Griesa
U.S. District Judge





UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----- x
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

AMNEAL PHARMACEUTICALS, LLC and
AMNEAL PHARMACEUTICALS OF NEW
YORK, LLC

Defendants.
----- x

12 Civ. 8115 (TPG)

ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC. and
BARR LABORATORIES, INC.

Defendant.
----- x

12 Civ. 8060 (TPG)

ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

IMPAX LABORATORIES, INC. and THORX
LABORATORIES, INC.

Defendants.
----- x

12 Civ. 8317 (TPG)

(captions continued on
following pages)

ORDER

Appx8321

-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	
	:	12 Civ. 8985 (TPG)
ACTAVIS INC. and ACTAVIS SOUTH	:	
ATLANTIC LLC,	:	
	:	
Defendants.	:	
	:	
-----	x	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	13 Civ. 435 (TPG)
	:	
IMPAX LABORATORIES, INC.,	:	
	:	
Defendants.	:	
	:	
-----	x	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	
	:	13 Civ. 436 (TPG)
ACTAVIS INC, ACTAVIS SOUTH	:	
ATLANTIC LLC, and WATSON	:	
PHARMACEUTICALS, INC.,	:	
	:	
Defendants.	:	
-----	x	

-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13 Civ. 3288 (TPG)
	:	
ROXANE LABORATORIES, INC.,	:	
	:	
Defendant.	:	
-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13 Civ. 4343 (TPG)
	:	13 Civ. 8597 (TPG)
SUN PHARMACEUTICAL INDUSTRIES,	:	
LTD.	:	
	:	
Defendant.	:	
-----	x	

ORDER

The court has filed, under seal, its findings of facts and conclusions of law regarding the bench trial for patent infringement which concluded on April 24, 2015. The decision refers to and incorporates confidential material. Thus, an unredacted copy of this decision has been emailed to each of the parties in the above captioned cases.

The parties are hereby directed to provide suggested redactions, if any, to the decision no later than Tuesday, August 18, 2015, at 12:00pm. They may do so by emailing black-line versions of the document to the court. Plaintiffs are encouraged, but not required, to submit their proposed redactions jointly. Defendants are encouraged, but not required, to do the same.

The court's ruling, as described more fully in the decision, is as follows. The court concludes that defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that defendants have failed to satisfy their burden of showing those claims to be invalid. The court concludes that defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid.


The court enters judgment in Endo's favor and enjoins defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents. Moreover, the court orders that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents. *See* 35 U.S.C. § 271(e)(4).

Because defendant Actavis is already on the market with its generic product, it shall have sixty days from the date of this order to comply. The court reserves decision on whether to award additional relief, including damages against defendant Actavis, pending further briefing from the parties.

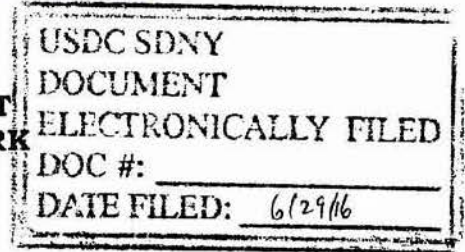
Endo's recently filed motion to strike Amneal's obviousness defense in case number 12-CV-8115 is moot. The clerk of court is directed to resolve all pending motions in the above captioned cases.

SO ORDERED.

Dated: New York, New York
August 14, 2015


Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**



-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

12-cv-8115 (TPG)

-against-

AMENDED JUDGMENT

AMNEAL PHARMACEUTICALS, LLC
and AMNEAL PHARMACEUTICALS OF
NEW YORK, LLC,

Defendants.

-----X

Whereas the above-captioned action having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiff Endo Pharmaceuticals Inc. ("Endo") argues that defendants, Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (collectively "Amneal" or "Defendants"), which are generic drug manufacturers, infringe on patents covering Endo's branded painkiller OPANA® ER by selling or seeking approval to sell generic versions of the drug; Defendants argue that their generic products, as described in their abbreviated New Drug Application ("ANDA"), do not and will not infringe the asserted claims of the patents asserted against each Defendant, and that in any event those patents are invalid; there are two patents-in-suit owned by Endo, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"), which recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; and the matter having come

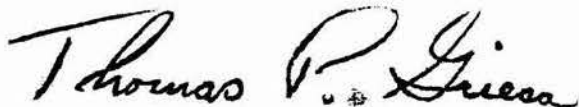
before the Honorable Thomas P. Griesa, United States District Judge, and the Court, on August 14, 2015, having rendered its Findings of Fact and Conclusions of Law the Court concluding that Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants having failed to satisfy their burden of showing those claims to be invalid, and for the reasons set forth with respect to co-defendant Roxane Laboratories Inc., in the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, the Court entering judgment in Endo's favor and permanently enjoining Defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283; moreover, the Court ordering that the effective date of approval of defendants' ANDA shall be no sooner than the expiration date of the '122 and '216 patents pursuant to 35 U.S.C. § 271(e)(4)(A); Endo's motion to strike Amneal's obviousness defense is moot; and the Court now having resolved all pending motions in the above-captioned case via its Order Resolving Post-Trial Motions (which is being entered in conjunction herewith), it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, that Defendants' generic products, as described in their ANDA, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants have failed to satisfy their burden of showing

those claims to be invalid; judgment is hereby entered in Endo's favor and enjoining Defendants pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 from the manufacture, use, offer to sell, or sale within the United States or importation into the United States of their generic products prior to the expiration of the '122 and '216 patents, said injunctive relief shall not cover any activities that are protected by the "safe harbor" provision of 35 U.S.C. § 271(e)(1); moreover, the Court orders pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of approval of defendants' ANDA shall be no sooner than the expiration date of the '122 and '216 patents; with respect to Defendants' counterclaims against the asserted claims of the '122 and '216 patents, judgment is hereby entered in Endo's favor on all counterclaims, except with respect to the counterclaims of non-infringement of the '216 patent as they relate to claims 40 and 42, as to which judgment is entered in Defendants' favor, and with respect to the counterclaims of invalidity of the '216 patent as they relate to claims 40 and 42, which are dismissed as moot; Endo's motion to strike Amneal's obviousness defense is moot.

SO ORDERED

Dated: New York, New York
June 29, 2016

Handwritten signature of Thomas P. Griesa in black ink.

Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**

USDC SDNY
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DOC #:
DATE FILED: 6/29/16

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

12-cv-8317 (TPG)

-against-

AMENDED JUDGMENT

IMPAX LABORATORIES, INC. and
THORX LABORATORIES, INC.,

Defendants.

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

13-cv-435 (TPG)

-against-

AMENDED JUDGMENT

IMPAX LABORATORIES, INC.,

Defendant.

-----X

Whereas the above-captioned actions having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Grünenthal GmbH ("Grünenthal") argue that defendants, Impax Laboratories Inc. and ThoRx Laboratories Inc. (collectively "Impax/ThoRx" or "Defendants"), which are generic drug manufacturers, infringe on patents covering Endo's branded painkiller OPANA® ER by selling or seeking approval to sell generic versions of the drug; Defendants argue that their generic products, as described in their abbreviated New Drug Applications ("ANDAs"), do not and will not infringe the

asserted claims of the patents asserted against Defendants, and that in any event those patents are invalid; there are a total of three patents-in-suit; Endo owns two of the patents asserted against all Defendants, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"), which recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; Grünenthal owns the third patent, United States Patent Number 8,309,060 ("the '060 Patent"), which describes an invention for drug-tablets so hard that they are difficult to abuse through crushing and snorting, and which also accommodate other barriers to abuse; and the matter having come before the Honorable Thomas P. Griesa, United States District Judge, and the Court, on August 14, 2015, having rendered its Findings of Fact and Conclusions of Law the Court concluding that all Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants having failed to satisfy their burden of showing those claims to be invalid; the Court concluding that Defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid based on obviousness, but have not satisfied their burden of showing that those claims are invalid on any other grounds, including under the provisions of 35 U.S.C. §§ 101, 102, and 112, and have not satisfied their burden of showing that the asserted claims of the '060 patent are invalid based on collateral estoppel; and for the reasons set forth with respect to co-defendant Roxane Laboratories Inc., in the Court's subsequent April 29, 2016 Omnibus

Opinion and the Court's Order Resolving Post-Trial Motions, the Court entering judgment in Endo's favor and permanently enjoining Defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283; moreover, the Court ordering that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents pursuant to 35 U.S.C. §271(e)(4)(A); and the Court now having resolved all pending motions in the above-captioned cases via its Order Resolving Post-Trial Motions (which is being entered in conjunction herewith), it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, that Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants have failed to satisfy their burden of showing those claims to be invalid; that Defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid based on obviousness; judgment is hereby entered in Endo's favor and enjoining Defendants pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 from the manufacture, use, offer to sell, or sale within the United States or importation into the United States of their generic products prior to the expiration of the '122 and '216 patents, said injunctive relief shall not cover any activities that are protected by the "safe harbor" provision of 35 U.S.C. §

271(e)(1); moreover, the Court orders pursuant to 35 U.S.C. §271(e)(4)(A) that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents; with respect to Defendants' counterclaims against the asserted claims of the '122 and '216 patents, judgment is hereby entered in Endo's favor on all counterclaims, except with respect to the counterclaims of non-infringement of the '216 patent as they relate to claims 40 and 42, as to which judgment is entered in Defendants' favor, and with respect to the counterclaims of invalidity of the '216 patent as they relate to claims 40 and 42, which are dismissed as moot; with respect to Defendants' counterclaims against the asserted claims of the '060 patent, judgment is hereby entered in Endo's and Grünenthal's favor on all counterclaims of non-infringement, in Defendants' favor on their counterclaims of invalidity based solely on obviousness but not on any other invalidity grounds, and in Endo's and Grünenthal's favor on all counterclaims of invalidity of the asserted claims of the '060 patent based on the provisions of 35 U.S.C. §§ 101, 102, and 112; the Court also rules in Endo's and Grünenthal's favor that the OxyContin invalidity decision regarding asserted claims of the '383 patent has no preclusive effect on the asserted claims of the '060 patent.

SO ORDERED

Dated: New York, New York
June 29, 2016



Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**

USDC SDNY
DOCUMENT
ELECTRONICALLY FILED
DOC #:
DATE FILED: 6/29/16

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

12-cv-8317 (TPG)

-against-

AMENDED JUDGMENT

IMPAX LABORATORIES, INC. and
THORX LABORATORIES, INC.,

Defendants.

-----X
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

13-cv-435 (TPG)

-against-

AMENDED JUDGMENT

IMPAX LABORATORIES, INC.,

Defendant.

-----X

Whereas the above-captioned actions having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Grünenthal GmbH ("Grünenthal") argue that defendants, Impax Laboratories Inc. and ThoRx Laboratories Inc. (collectively "Impax/ThoRx" or "Defendants"), which are generic drug manufacturers, infringe on patents covering Endo's branded painkiller OPANA® ER by selling or seeking approval to sell generic versions of the drug; Defendants argue that their generic products, as described in their abbreviated New Drug Applications ("ANDAs"), do not and will not infringe the

asserted claims of the patents asserted against Defendants, and that in any event those patents are invalid; there are a total of three patents-in-suit; Endo owns two of the patents asserted against all Defendants, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"), which recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; Grünenthal owns the third patent, United States Patent Number 8,309,060 ("the '060 Patent"), which describes an invention for drug-tablets so hard that they are difficult to abuse through crushing and snorting, and which also accommodate other barriers to abuse; and the matter having come before the Honorable Thomas P. Griesa, United States District Judge, and the Court, on August 14, 2015, having rendered its Findings of Fact and Conclusions of Law the Court concluding that all Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants having failed to satisfy their burden of showing those claims to be invalid; the Court concluding that Defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid based on obviousness, but have not satisfied their burden of showing that those claims are invalid on any other grounds, including under the provisions of 35 U.S.C. §§ 101, 102, and 112, and have not satisfied their burden of showing that the asserted claims of the '060 patent are invalid based on collateral estoppel; and for the reasons set forth with respect to co-defendant Roxane Laboratories Inc., in the Court's subsequent April 29, 2016 Omnibus

Opinion and the Court's Order Resolving Post-Trial Motions, the Court entering judgment in Endo's favor and permanently enjoining Defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283; moreover, the Court ordering that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents pursuant to 35 U.S.C. §271(e)(4)(A); and the Court now having resolved all pending motions in the above-captioned cases via its Order Resolving Post-Trial Motions (which is being entered in conjunction herewith), it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, that Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants have failed to satisfy their burden of showing those claims to be invalid; that Defendants infringe the asserted claims of the '060 Patent, but that they have satisfied their burden and shown those claims to be invalid based on obviousness; judgment is hereby entered in Endo's favor and enjoining Defendants pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 from the manufacture, use, offer to sell, or sale within the United States or importation into the United States of their generic products prior to the expiration of the '122 and '216 patents, said injunctive relief shall not cover any activities that are protected by the "safe harbor" provision of 35 U.S.C. §

271(e)(1); moreover, the Court orders pursuant to 35 U.S.C. §271(e)(4)(A) that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents; with respect to Defendants' counterclaims against the asserted claims of the '122 and '216 patents, judgment is hereby entered in Endo's favor on all counterclaims, except with respect to the counterclaims of non-infringement of the '216 patent as they relate to claims 40 and 42, as to which judgment is entered in Defendants' favor, and with respect to the counterclaims of invalidity of the '216 patent as they relate to claims 40 and 42, which are dismissed as moot; with respect to Defendants' counterclaims against the asserted claims of the '060 patent, judgment is hereby entered in Endo's and Grünenthal's favor on all counterclaims of non-infringement, in Defendants' favor on their counterclaims of invalidity based solely on obviousness but not on any other invalidity grounds, and in Endo's and Grünenthal's favor on all counterclaims of invalidity of the asserted claims of the '060 patent based on the provisions of 35 U.S.C. §§ 101, 102, and 112; the Court also rules in Endo's and Grünenthal's favor that the OxyContin invalidity decision regarding asserted claims of the '383 patent has no preclusive effect on the asserted claims of the '060 patent.

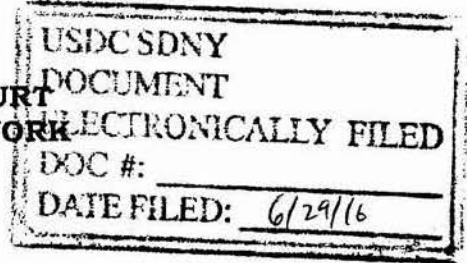
SO ORDERED

Dated: New York, New York
June 29, 2016



Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**



-----X
ENDO PHARMACEUTICALS INC.,

Plaintiff,

13-cv-3288 (TPG)

-against-

AMENDED JUDGMENT

ROXANE LABORATORIES INC.,

Defendant.

-----X

Whereas the above-captioned action having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiff Endo Pharmaceuticals Inc. ("Endo") argues that defendant, Roxane Laboratories, Inc. ("Roxane" or "Defendant"), which is a generic drug manufacturer, infringes on patents covering Endo's branded painkiller OPANA® ER by selling or seeking approval to sell generic versions of the drug; Defendant argues that its generic products, as described in its abbreviated New Drug Application ("ANDAs"), do not and will not infringe the asserted claims of the asserted patents, and that in any event those patents are invalid; Defendant also asserted other statutory and equitable defenses; there are two patents-in-suit owned by Endo, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"), which recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; and the matter having come before the Honorable Thomas P. Griesa, United States District Judge, and the Court, on August 14, 2015, having rendered its Findings of Fact and Conclusions of Law the Court concluding that

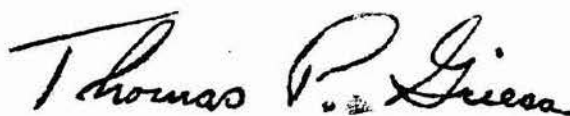
Defendant's generic products, as described in its ANDA, infringe all but two of the asserted claims of the '122 and '216 patents; the Court entering judgment in Endo's favor and enjoining Defendant from making or selling its generic products prior to the expiration of the '122 and '216 patents pursuant to 35 U.S.C. § 283; moreover, for the reasons set forth in the Court's subsequent April 29, 2016 Omnibus Opinion addressing post-trial motions filed by the parties, the Court declines ordering that the effective date of approval of Defendant's ANDA shall be no sooner than the expiration date of the '122 and '216 patents pursuant to 35 U.S.C. § 271(e)(4)(A); and the Court now having resolved all pending motions in the above-captioned case via its Order Resolving Post-Trial Motions (which is being entered in conjunction herewith), it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, and the Court's April 29, 2016 Omnibus Opinion, that Defendant's generic products, as described in its ANDA, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendant has failed to satisfy its burden of showing those claims to be invalid; judgment is hereby entered in Endo's favor and enjoining Defendant pursuant to 35 U.S.C. § 283 from the manufacture, use, offer to sell, or sale within the United States or importation into the United States of its generic products prior to the expiration of the '122 and '216 patents, said injunctive relief shall not cover any activities that are protected by the "safe harbor" provision of 35 U.S.C. § 271(e)(1); with respect to Defendant's counterclaims against the asserted claims of the '122 and '216 patents,

judgment is hereby entered in Endo's favor on all counterclaims, except with respect to the counterclaims of non-infringement of the '216 patent as they relate to claims 40 and 42, as to which judgment is entered in Defendant's favor, and with respect to the counterclaims of invalidity of the '216 patent as they relate to claims 40 and 42, which are dismissed as moot.

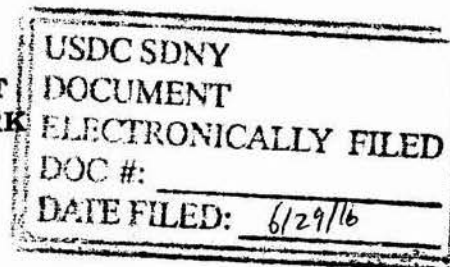
SO ORDERED

Dated: New York, New York
June 29, 2016

A handwritten signature in black ink, reading "Thomas P. Griesa". The signature is written in a cursive, flowing style. The first name "Thomas" is written in a larger, more prominent script, followed by "P." and "Griesa".

Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**



-----X
ENDO PHARMACEUTICALS INC.,

Plaintiff,

-against-

13-cv-4343 (TPG)

13-cv-8597 (TPG)

SUN PHARMACEUTICALS
INDUSTRIES, LTD., RANBAXY INC.,
and RANBAXY PHARMACEUTICALS
INC.,

AMENDED JUDGMENT

Defendants.

-----X

Whereas the above-captioned actions having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiff Endo Pharmaceuticals Inc. ("Endo") argues that defendants, Sun Pharmaceuticals Industries, Ltd., Ranbaxy Inc., and Ranbaxy Pharmaceuticals Inc. (collectively "Sun" or "Defendants"), which are generic drug manufacturers, infringe on patents covering Endo's branded painkiller OPANA® ER by selling or seeking approval to sell generic versions of the drug; Defendants argue that their generic products, as described in their abbreviated New Drug Applications ("ANDAs"), do not and will not infringe the asserted claims of the patents asserted against each Defendant, and that in any event those patents are invalid; there are two patents-in-suit owned by Endo, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"), which recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; and the matter having come before the Honorable Thomas P. Griesa, United States District Judge, and the

Court, on August 14, 2015, having rendered its Findings of Fact and Conclusions of Law the Court concluding that all Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants having failed to satisfy their burden of showing those claims to be invalid, and for the reasons set forth with respect to co-defendant Roxane Laboratories Inc., in the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, the Court entering judgment in Endo's favor and permanently enjoining Defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283; moreover, the Court ordering that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents pursuant to 35 U.S.C. § 271(e)(4)(A); and the Court now having resolved all pending motions in the above-captioned cases via its Order Resolving Post-Trial Motions (which is being entered in conjunction herewith), it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, that Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants have failed to satisfy their burden of showing those claims to be invalid; judgment is hereby entered in Endo's favor and

enjoining Defendants pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 from the manufacture, use, offer to sell, or sale within the United States or importation into the United States of their generic products prior to the expiration of the '122 and '216 patents, said injunctive relief shall not cover any activities that are protected by the "safe harbor" provision of 35 U.S.C. § 271(e)(1); moreover, the Court orders pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents; with respect to Defendants' counterclaims against the asserted claims of the '122 and '216 patents, judgment is hereby entered in Endo's favor on all counterclaims, except with respect to the counterclaims of non-infringement of the '216 patent as they relate to claims 40 and 42, as to which judgment is entered in Defendants' favor, and with respect to the counterclaims of invalidity of the '216 patent as they relate to claims 40 and 42, which are dismissed as moot.

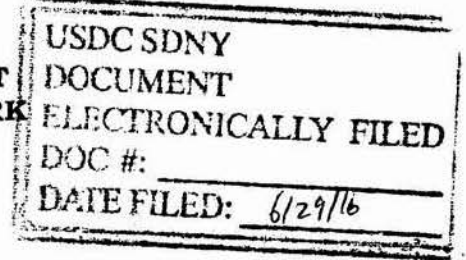
SO ORDERED

Dated: New York, New York
June 29, 2016



Thomas P. Griesa
U.S. District Judge

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK**



-----X
ENDO PHARMACEUTICALS INC.,

Plaintiff,

-against-

13-cv-4343 (TPG)

13-cv-8597 (TPG)

SUN PHARMACEUTICALS
INDUSTRIES, LTD., RANBAXY INC.,
and RANBAXY PHARMACEUTICALS
INC.,

AMENDED JUDGMENT

Defendants.

-----X

Whereas the above-captioned actions having come before this Court, and on April 24, 2015 marked the conclusion of a five-week bench trial for patent infringement; Plaintiff Endo Pharmaceuticals Inc. ("Endo") argues that defendants, Sun Pharmaceuticals Industries, Ltd., Ranbaxy Inc., and Ranbaxy Pharmaceuticals Inc. (collectively "Sun" or "Defendants"), which are generic drug manufacturers, infringe on patents covering Endo's branded painkiller OPANA® ER by selling or seeking approval to sell generic versions of the drug; Defendants argue that their generic products, as described in their abbreviated New Drug Applications ("ANDAs"), do not and will not infringe the asserted claims of the patents asserted against each Defendant, and that in any event those patents are invalid; there are two patents-in-suit owned by Endo, United States patent numbers 8,309,122 ("the '122 Patent") and 8,329,216 ("the '216 Patent"), which recite a controlled release formulation of the painkilling opioid oxymorphone suitable for twelve-hour dosing; and the matter having come before the Honorable Thomas P. Griesa, United States District Judge, and the

Court, on August 14, 2015, having rendered its Findings of Fact and Conclusions of Law the Court concluding that all Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants having failed to satisfy their burden of showing those claims to be invalid, and for the reasons set forth with respect to co-defendant Roxane Laboratories Inc., in the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, the Court entering judgment in Endo's favor and permanently enjoining Defendants from making or selling their generic products prior to the expiration of the '122 and '216 patents pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283; moreover, the Court ordering that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents pursuant to 35 U.S.C. § 271(e)(4)(A); and the Court now having resolved all pending motions in the above-captioned cases via its Order Resolving Post-Trial Motions (which is being entered in conjunction herewith), it is,

ORDERED, ADJUDGED AND DECREED: That for the reasons stated in the Court's Findings of Fact and Conclusions of Law dated August 14, 2015, the Court's subsequent April 29, 2016 Omnibus Opinion and the Court's Order Resolving Post-Trial Motions, that Defendants' generic products, as described in their ANDAs, infringe all but two of the asserted claims of the '122 and '216 patents, and that Defendants have failed to satisfy their burden of showing those claims to be invalid; judgment is hereby entered in Endo's favor and

enjoining Defendants pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 from the manufacture, use, offer to sell, or sale within the United States or importation into the United States of their generic products prior to the expiration of the '122 and '216 patents, said injunctive relief shall not cover any activities that are protected by the "safe harbor" provision of 35 U.S.C. § 271(e)(1); moreover, the Court orders pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of approval of defendants' ANDAs shall be no sooner than the expiration date of the '122 and '216 patents; with respect to Defendants' counterclaims against the asserted claims of the '122 and '216 patents, judgment is hereby entered in Endo's favor on all counterclaims, except with respect to the counterclaims of non-infringement of the '216 patent as they relate to claims 40 and 42, as to which judgment is entered in Defendants' favor, and with respect to the counterclaims of invalidity of the '216 patent as they relate to claims 40 and 42, which are dismissed as moot.

SO ORDERED

Dated: New York, New York
June 29, 2016



Thomas P. Griesa
U.S. District Judge

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----- x
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

AMNEAL PHARMACEUTICALS, LLC and
AMNEAL PHARMACEUTICALS OF NEW
YORK, LLC,

Defendants.
----- x

ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC. and
BARR LABORATORIES, INC.,

Defendants.
----- x

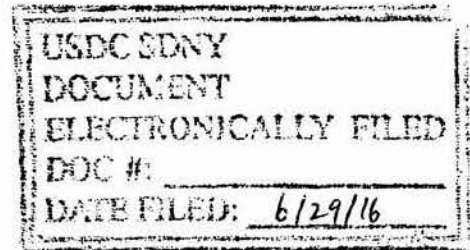
ENDO PHARMACEUTICALS INC. and
GRÜNENTHAL GMBH,

Plaintiffs,

v.

IMPAX LABORATORIES, INC. and THORX
LABORATORIES, INC.,

Defendants.
----- x



12-cv-8115 (TPG)

12-cv-8060 (TPG)

12-cv-8317 (TPG)

(captions continued on
following pages)

-----	X	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	
	:	12-cv-8985 (TPG)
ACTAVIS INC. and ACTAVIS SOUTH	:	
ATLANTIC LLC,	:	
	:	
Defendants.	:	
-----	X	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	13-cv-435 (TPG)
	:	
IMPAX LABORATORIES, INC.,	:	
	:	
Defendant.	:	
-----	X	
ENDO PHARMACEUTICALS INC. and	:	
GRÜNENTHAL GMBH,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	
	:	13-cv-436 (TPG)
ACTAVIS INC, ACTAVIS SOUTH	:	
ATLANTIC LLC, and WATSON	:	
PHARMACEUTICALS, INC.,	:	
	:	
Defendants.	:	
-----	X	

-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13-cv-3288 (TPG)
	:	
ROXANE LABORATORIES, INC.,	:	
	:	
Defendant.	:	
	:	
-----	x	
ENDO PHARMACEUTICALS INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	13-cv-4343 (TPG)
	:	13-cv-8597 (TPG)
SUN PHARMACEUTICAL INDUSTRIES,	:	
LTD.	:	
	:	
Defendant.	:	
-----	x	

ORDER RESOLVING POST-TRIAL MOTIONS

Following a five-week bench trial on patent infringement, the court found that each defendant had infringed on asserted claims of two patents. The parties then filed a series of post-trial motions, which the court will now resolve.

Background

After trial ended in April 2015, the court issued findings of fact and conclusions of law on August 14, 2015. The court's essential holding was that defendants had infringed on asserted claims of two patents. Accordingly, the court entered judgment and enjoined defendants from making or selling their generic products prior to the expiration of the patents. The court also ordered

that the effective date of approval of defendants' ANDAs could be no sooner than the expiration of the patents.

Following entry of judgment, the parties filed post-trial motions. Defendants Actavis Inc. and Actavis South Atlantic, LLC ("Actavis") filed a Rule 59(e) motion to amend the judgment in case 12-cv-8985. Actavis asked the court to address the factors for a permanent injunction set forth in *eBay Inc. v. MercExchange L.L.C.*, 547 U.S. 388 (2006), and to find that a permanent injunction was not warranted on the trial record. Actavis also asked the court to find that plaintiffs were not entitled to relief under 35 U.S.C. § 271(e)(4)(A) as to Actavis's ANDA. Defendant Roxane Laboratories, Inc. ("Roxane") filed its own Rule 59(e) motion to amend the judgment in case 13-cv-3288. Like Actavis, Roxane asked the court to deny relief under § 271(e)(4)(A) as to Roxane's ANDA.

Plaintiffs filed motions of their own. First, plaintiffs filed a Rule 60(a) motion to correct the judgments in all cases, asking the court to revise the description of the scope of injunctive relief, address findings on defendants' counterclaims, and fix minor clerical mistakes. Defendants largely assented to the proposed corrections, though some defendants opposed certain aspects of the motion. Plaintiff Endo Pharmaceuticals Inc. ("Endo") then filed a separate Rule 52(b) motion to amend the judgments in all cases, asking the court to address explicitly the *eBay* factors underling the permanent injunctive relief entered against all defendants.

In an Omnibus Opinion issued on April 29, 2016, the court ruled that Endo was not entitled to relief under § 271(e)(4)(A) against Actavis in case 12-cv-8985 and Roxane in case 13-cv-3288. The court therefore declined to alter the

effective dates of Actavis's and Roxane's ANDAs and indicated that it would amend the judgments accordingly. The court did, however, exercise its general equitable power to enjoin those defendants from making or selling their generic products prior to the expiration of the relevant patents, finding that the *eBay* factors supported entry of injunctive relief.

The Omnibus Opinion noted that the ruling as to Actavis and Roxane did not alter the court's original grant of relief under § 271(e)(4)(A) in all other cases. But in a separate order filed that same day, the court invited briefing in those other cases as to whether the *eBay* factors supported entry of injunctions against the remaining defendants. The parties have now submitted briefing, and the court will address all the post-trial motions.

Discussion

As an initial matter, the court notes that its Omnibus Opinion addressed plaintiffs' Rule 60(a) motion, finding that certain of the proposed corrections helped clarify the court's intent at the time of issuing the original judgment and did not rely on new evidence or reasoning. Accordingly, the amended judgments will incorporate those corrections.

The Omnibus Opinion also resolved Actavis's and Roxane's Rule 59(e) motions and Endo's Rule 52(b) motion as it pertained to Actavis in case 12-cv-8985 and Roxane in case 13-cv-3288. The court will amend the judgments accordingly in separate docket entries.

As to how Endo's Rule 52(b) motion fares in all other cases, the court now finds that, for the same reasons given in the Omnibus Opinion with respect to Roxane, the *eBay* factors support injunctions against each of the remaining

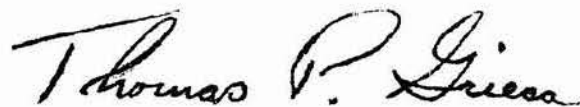
defendants pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283. Endo sufficiently proved that it would be irreparably harmed by the entry of additional generics into the market—in the form of lost market share, profits, and goodwill—and that this harm goes beyond financial harm to include reputational, organizational, and administrative harm. Money damages would be inadequate to compensate Endo for defendants' infringements, including because Endo demonstrated it would suffer difficult-to-quantify harms such as reductions in sales force and decreased investments in research and development. Moreover, the balance of hardships clearly favors Endo, particularly given that defendants have made no showing of any alleged hardship from the imposition of a permanent injunction. Granting the injunction would also serve the public interest by, among other things, protecting valid patent rights and thereby encouraging innovation and further research and development. Ultimately, the court sees no reason why the findings as to Roxane in the Omnibus Opinion do not apply with equal force to the remaining defendants.

Conclusion

This order and the accompanying amended judgments resolve all open issues related to the parties' post-trial motions.

SO ORDERED

Dated: New York, New York
June 29, 2016



Thomas P. Griesa
U.S. District Judge



US008309122B2

(12) **United States Patent**
Kao et al.

(10) **Patent No.:** **US 8,309,122 B2**
(45) **Date of Patent:** ***Nov. 13, 2012**

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

(58) **Field of Classification Search** None
See application file for complete search history.

(75) Inventors: **Huai-Hung Kao**, Syosset, NY (US);
Anand R. Baichwal, Wappingers Falls,
NY (US); **Troy McCall**, Smyrna, GA
(US); **David Lee**, Chadds Ford, PA (US)

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(Continued)

(21) Appl. No.: **11/680,432**

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(22) Filed: **Feb. 28, 2007**

CA 2314896 A1 7/1999

(Continued)

(65) **Prior Publication Data**

US 2007/0134328 A1 Jun. 14, 2007

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(Continued)

Related U.S. Application Data

(63) Continuation of application No. 10/190,192, filed on
Jul. 3, 2002.

(60) Provisional application No. 60/303,357, filed on Jul. 6,
2001, provisional application No. 60/329,432, filed on
Oct. 15, 2001, provisional application No. 60/329,444,
filed on Oct. 15, 2001, provisional application No.
60/329,445, filed on Oct. 15, 2001.

Primary Examiner — Lakshmi Channavajjala

(74) *Attorney, Agent, or Firm* — Mayer Brown LLP

(51) **Int. Cl.**

A61K 9/22 (2006.01)

A61K 9/34 (2006.01)

A61K 9/36 (2006.01)

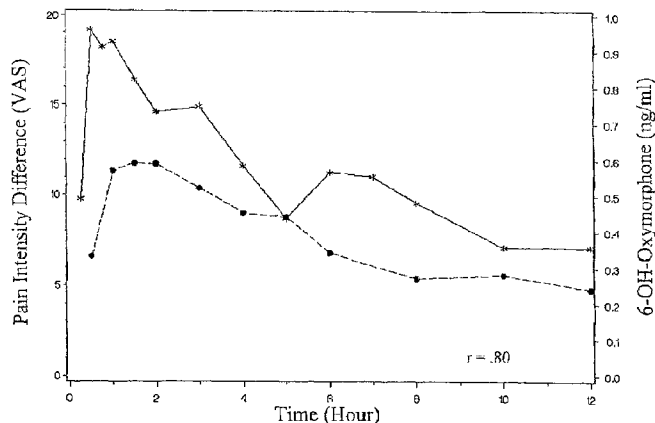
(57) **ABSTRACT**

The invention pertains to a method of relieving pain by
administering a controlled release pharmaceutical tablet con-
taining oxymorphone which produces a mean minimum
blood plasma level 12 to 24 hours after dosing, as well as the
tablet producing the sustained pain relief.

(52) **U.S. Cl.** **424/464; 424/468; 424/470; 424/479;**
424/481; 424/482; 424/486

20 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

US 8,309,122 B2

Page 2

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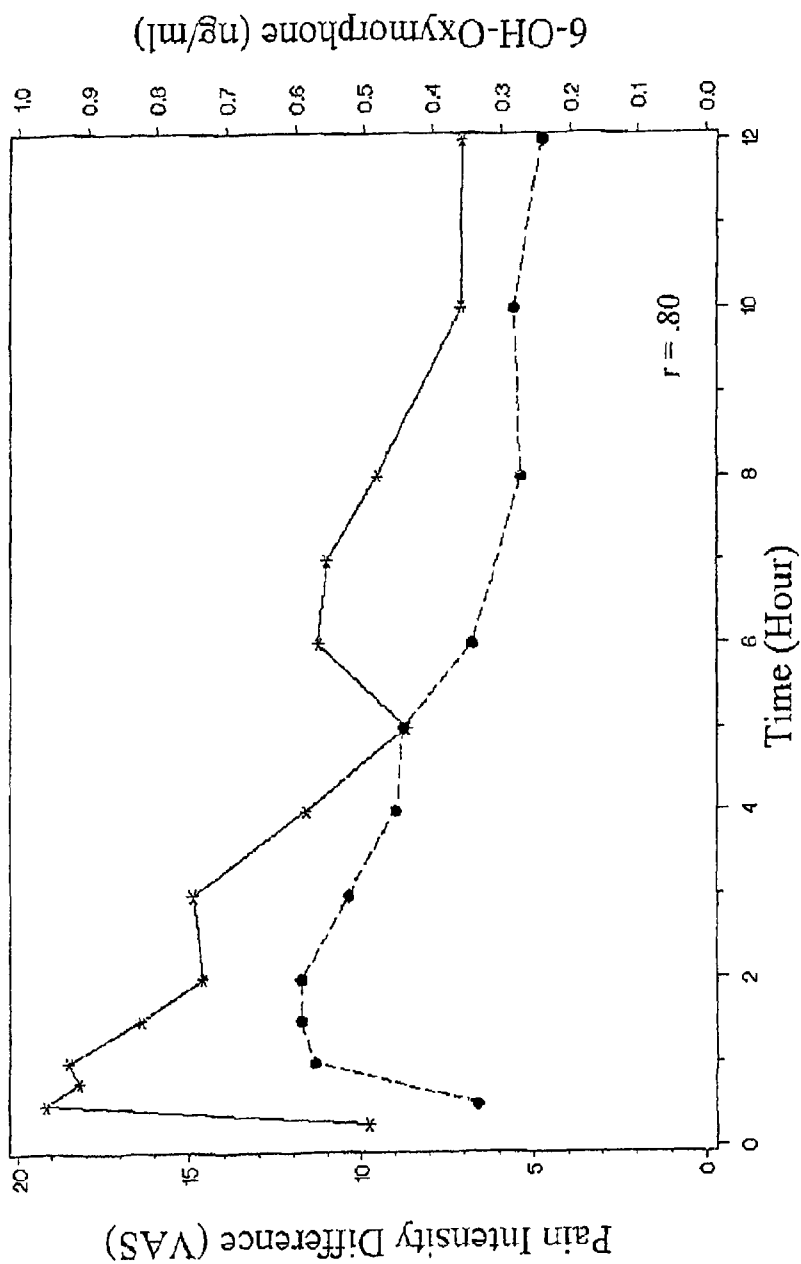
U.S. Patent

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PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

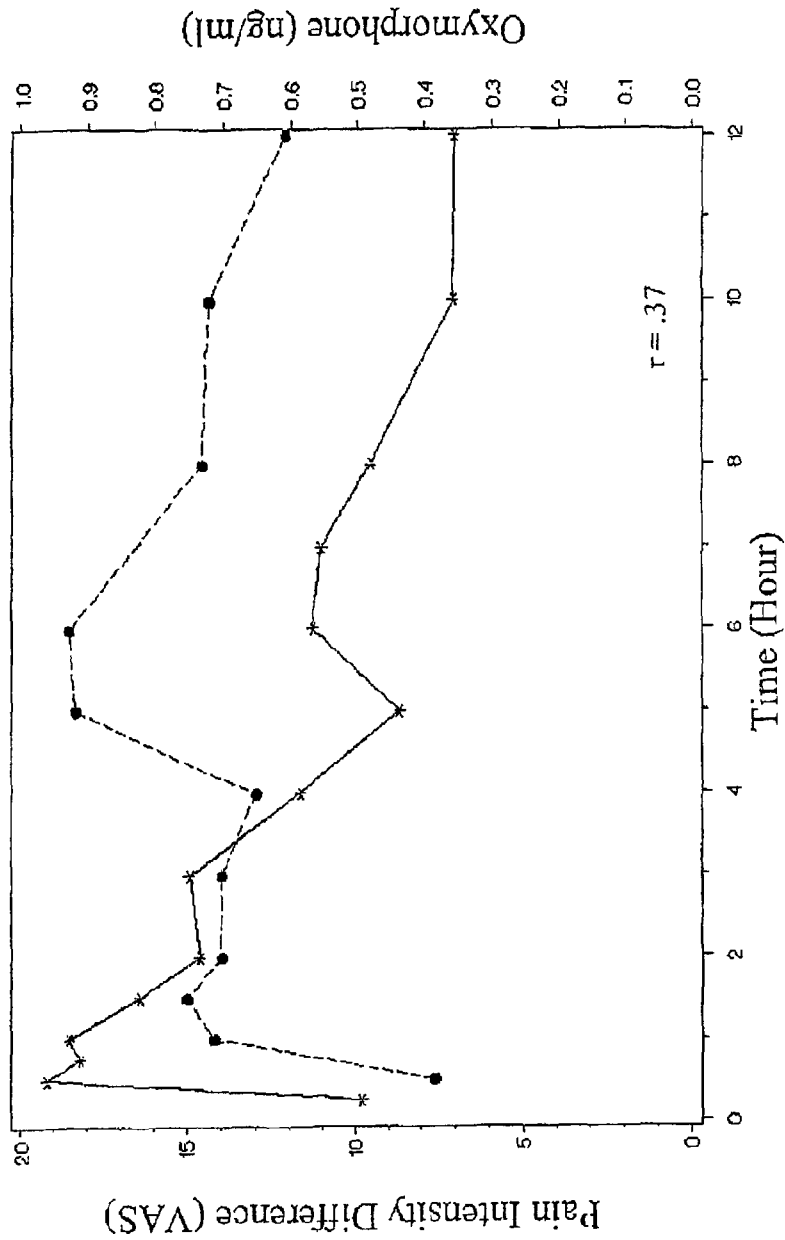
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PK Profile for Oxymorphone with PID Scores



* Pain Intensity Difference • Oxymorphone Plasma Concentrations

Fig. 2

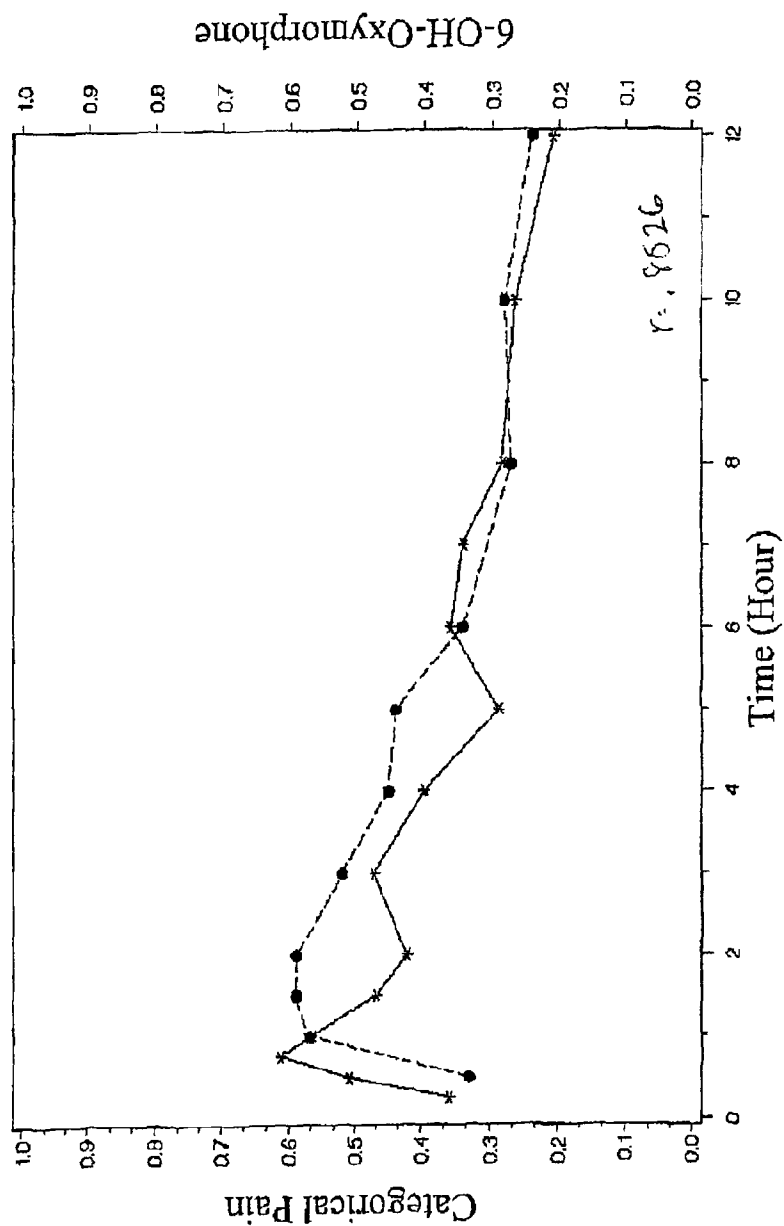
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PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores



* Categorical Pain ● 6-OH Oxymorphone Plasma Concentrations
FIG. 3

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PK Profile for Oxymorphone with Categorical Pain Scores

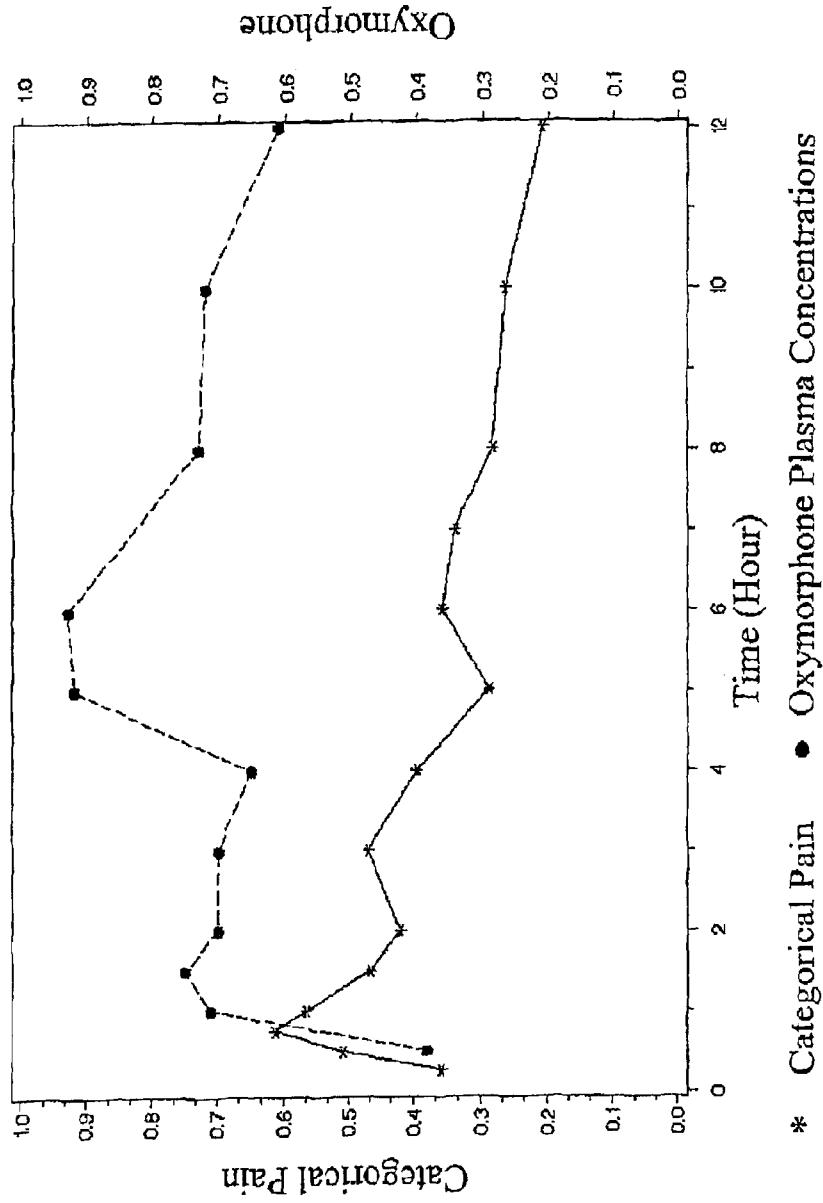


Fig. 4

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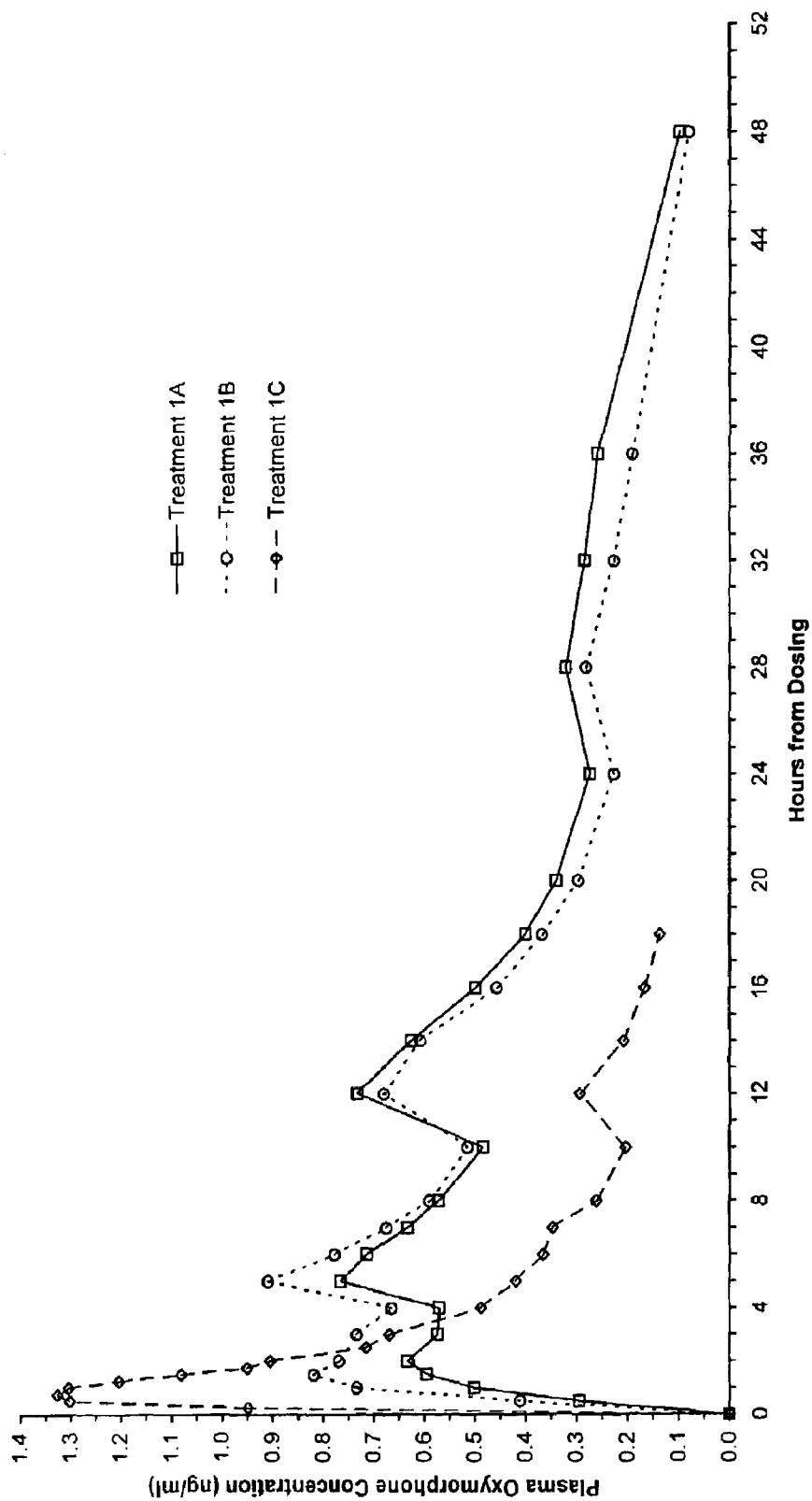


Figure 5

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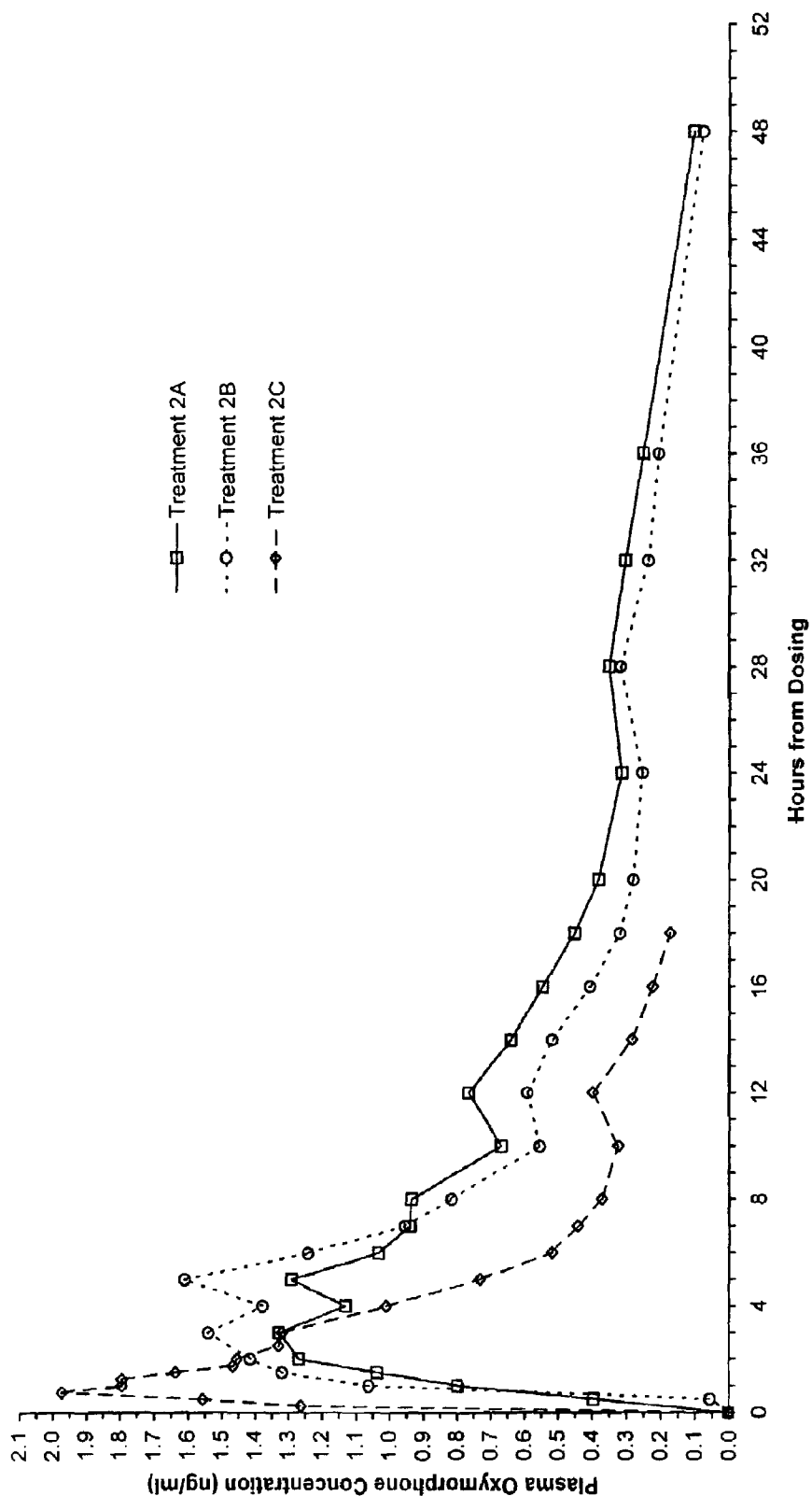


Figure 6

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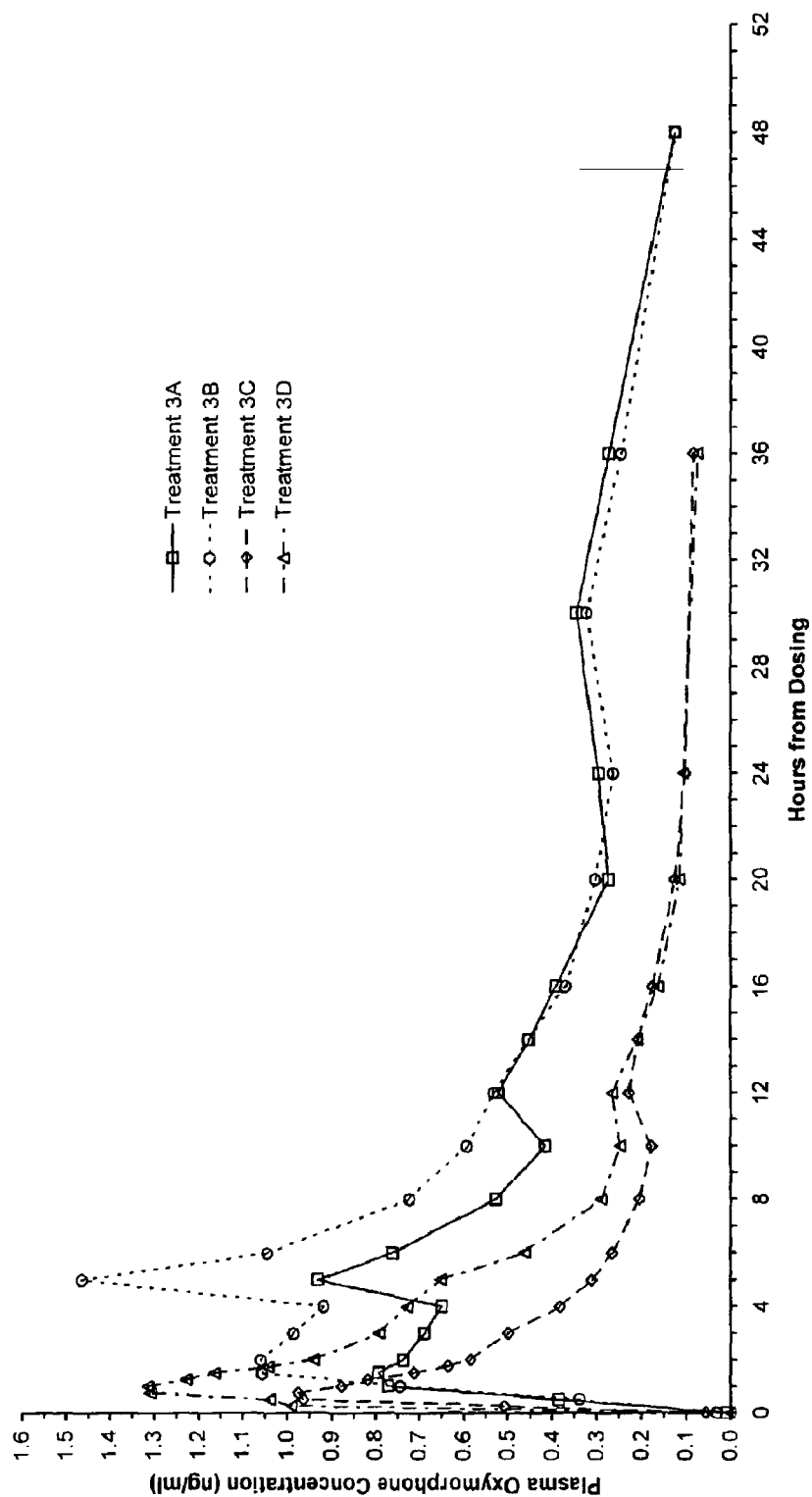


Figure 7

Appx275

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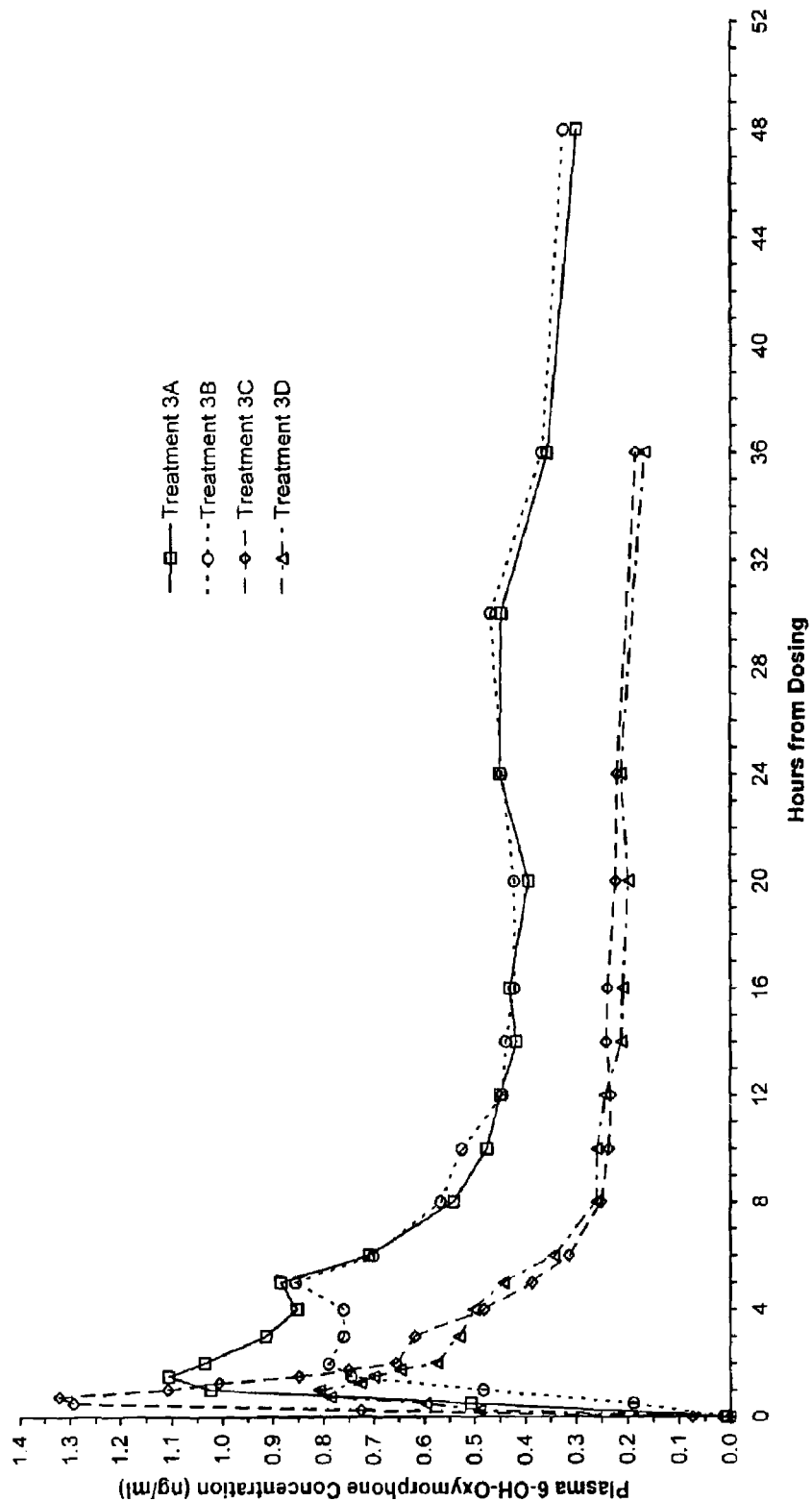


Figure 8

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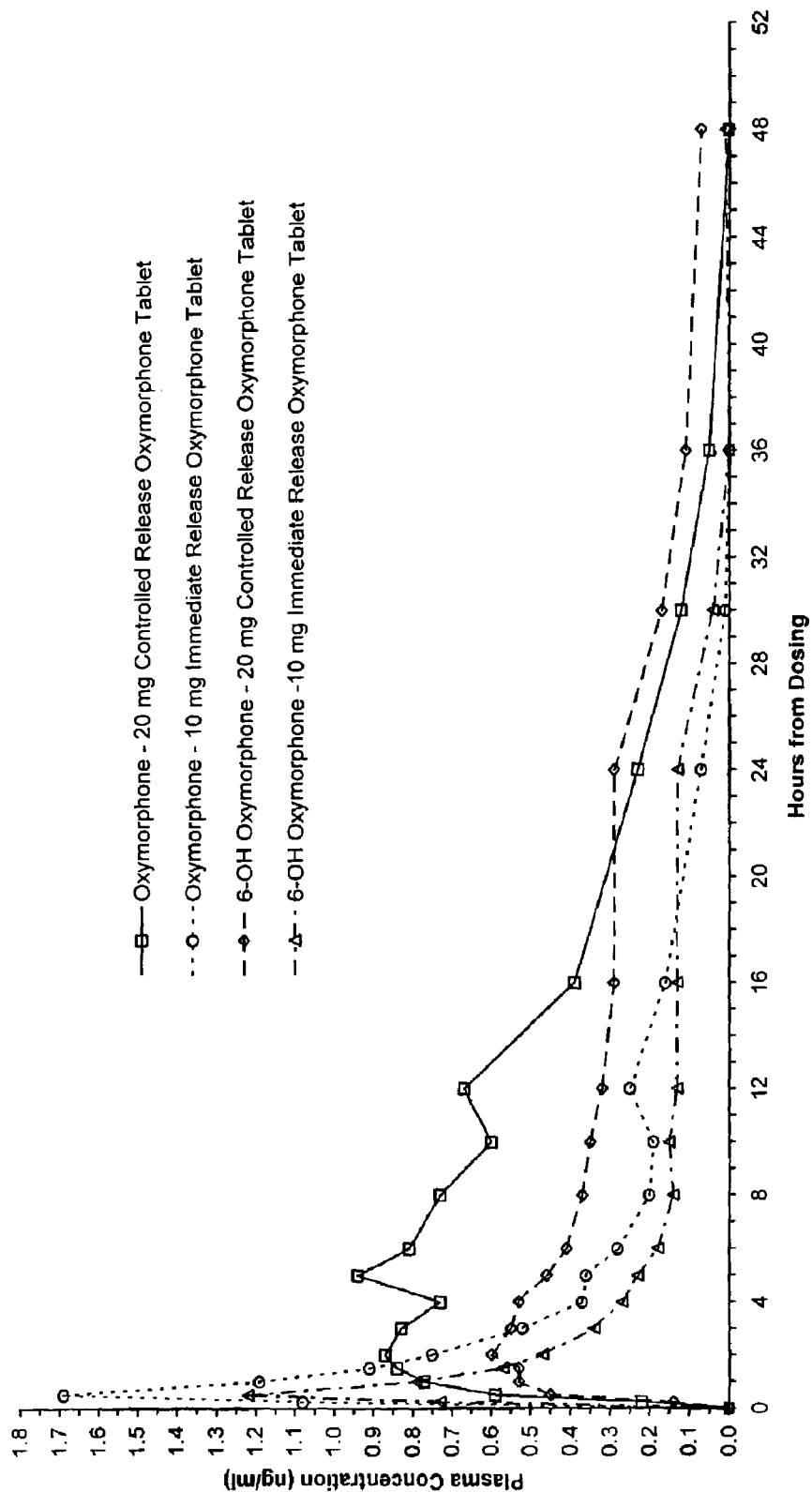


Figure 9

Appx277

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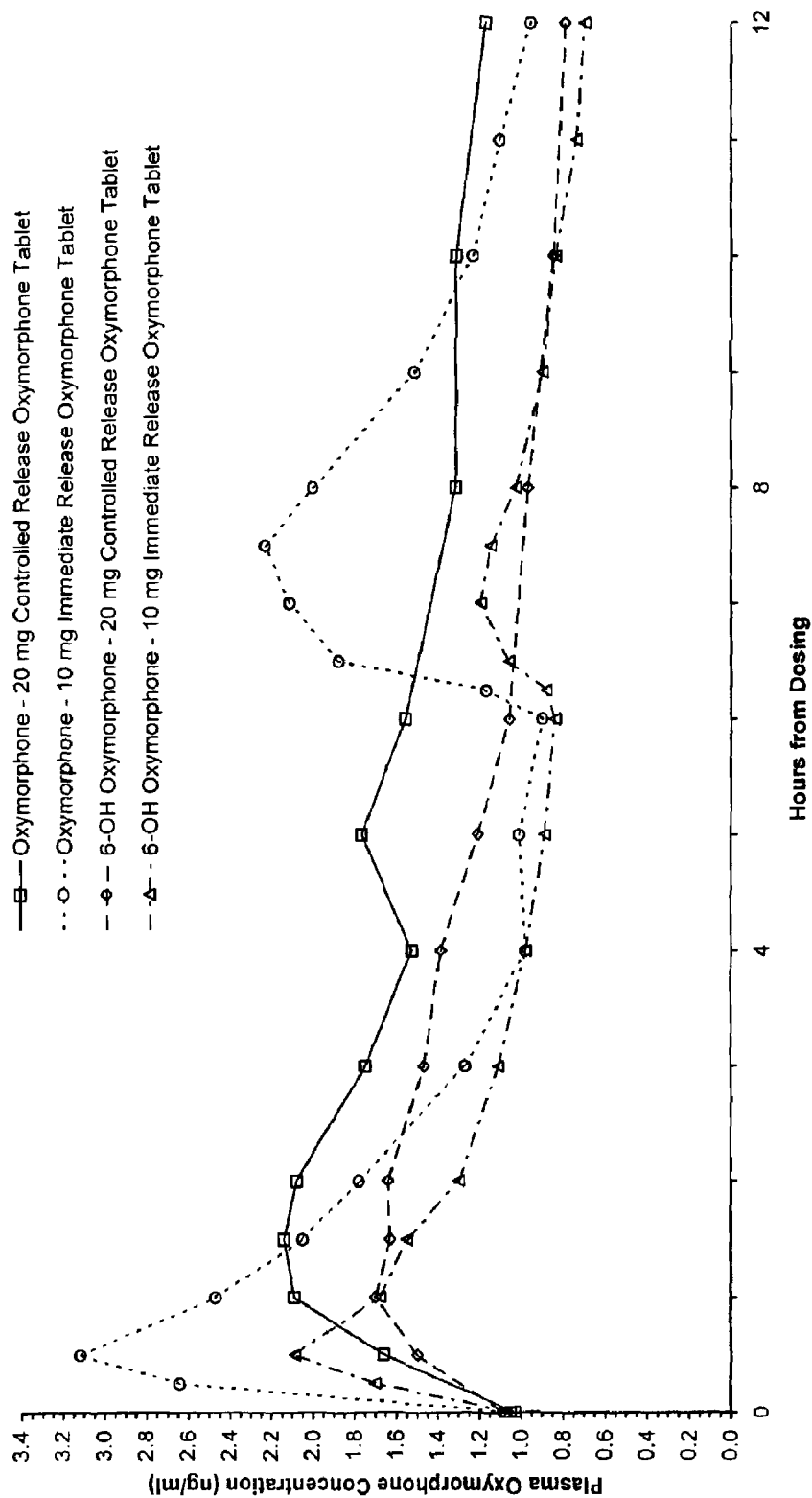


Figure 10

Appx278

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OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**RELATED APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6- α - and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer

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patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. 2 is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. 3 is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. 4 is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. 5 is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. 6 is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. 7 is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. 8 is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. 9 is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. 10 is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

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ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values

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reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylene-sulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

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It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. 1-2 show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical

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ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

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and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^5$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacetylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially

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insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

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porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System		
Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10) ¹	(20.0) ¹
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

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TABLE 2

Sample Tablets of Differing Strengths					
Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, NF	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions			
Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets			
Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bio-availability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

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trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.
$AUC_{(0-inf)}$	Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)} = AUC_{(0-t)} + Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.
$AUC_{(0-24)}$	Partial area under the drug concentration-time curve from time zero to 24 hours.
C_{max}	Maximum observed drug concentration.
T_{max}	Time of the observed maximum drug concentration.
K_{el}	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max} , $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive

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statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1—Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C	
0	0.000	0.000	0.0000	
0.25			0.9489	
0.5	0.2941	0.4104	1.3016	
0.75			1.3264	
1	0.5016	0.7334	1.3046	
1.25			1.2041	
1.5	0.5951	0.8192	1.0813	
1.75			0.9502	
2	0.6328	0.7689	0.9055	
2.5			0.7161	
3	0.5743	0.7341	0.6689	
4	0.5709	0.6647	0.4879	
5	0.7656	0.9089	0.4184	
6	0.7149	0.7782	0.3658	
7	0.6334	0.6748	0.3464	
8	0.5716	0.5890	0.2610	
10	0.4834	0.5144	0.2028	
12	0.7333	0.6801	0.2936	
14	0.6271	0.6089	0.2083	
16	0.4986	0.4567	0.1661	
18	0.4008	0.3674	0.1368	
20	0.3405	0.2970		
24	0.2736	0.2270		
28	0.3209	0.2805		
32	0.2846	0.2272		
36	0.2583	0.1903		
48	0.0975	0.0792		

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

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Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1						
	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61
Units:						
C_{max} in ng/ml,						
T_{max} in hours,						
AUC in ng * hr/ml,						
$T_{1/2el}$ in hours.						

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$		
F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 ± 0.203	1.121 ± 0.211	1.108 ± 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-18h)}$		
F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 ± 0.098	0.783 ± 0.117	0.944 ± 0.110

Study 2 Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast fol-

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lowed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C	
0	0.000	0.000	0.0000	
0.25			1.263	
0.5	0.396	.0553	1.556	
0.75			1.972	
1	0.800	1.063	1.796	
1.25			1.795	
1.5	1.038	1.319	1.637	
1.75			1.467	
2	1.269	1.414	1.454	
2.5			1.331	
3	1.328	1.540	1.320	
4	1.132	1.378	1.011	
5	1.291	1.609	0.731	
6	1.033	1.242	0.518	
7	0.941	0.955	0.442	
8	0.936	0.817	0.372	
10	0.669	0.555	0.323	
12	0.766	0.592	0.398	
14	0.641	0.519	0.284	
16	0.547	0.407	0.223	
18	0.453	0.320	0.173	
20	0.382	0.280		
24	0.315	0.254		
28	0.352	0.319		
32	0.304	0.237		
36	0.252	0.207		
48	0.104	0.077		

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2						
	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

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TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2						
	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
AUC _(0-inf)	25.28	5.736	23.62	5.202	24.73	6.616
T _{1/2rel}	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng • hr/ml,
T_{1/2rel} in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on AUC _(0-∞)		
F _{rel} (2A vs. 2C)	F _{rel} (2B vs. 2C)	F _{rel} (2A vs. 2B)
1.052 ± 0.187	0.949 ± 0.154	1.148 ± 0.250

TABLE 12

Relative bioavailability Determination Based on AUC _(0-∞)		
F _{rel} (2A vs. 2C)	F _{rel} (2B vs. 2C)	F _{rel} (2A vs. 2B)
0.690 ± 0.105	0.694 ± 0.124	1.012 ± 0.175

As may be seen from tables 5 and 10 and FIGS. 1 and 2, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T_{max} much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3—One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

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Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 7. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

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TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3								
	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.56	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-24)}$			
F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
1.040 ± 0.1874	0.8863 ± 0.2569	1.368 ± 0.4328	1.169 ± 0.2041

TABLE 16

Relative Bioavailability Determination Based on $AUC_{(0-24)}$			
F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
0.9598 ± 0.2151	0.8344 ± 0.100	1.470 ± 0.3922	1.299 ± 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max} , but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max} (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C).

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From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxyoxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max} was later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under the fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxyoxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-values duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxyoxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normal-

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ized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicated similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment.

Bioavailability of 6-hydroxyoxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent

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TABLE 17-continued

Mean Plasma Concentration vs. Time (ng/ml)				
6-Hydroxyoxymorphone				
Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma 6-Hydroxymorphone for Study 3								
	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(0-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(0-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 8. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml)				
6-Hydroxyoxymorphone				
Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877

Study 4—Controlled Release 20 mg vs. Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg controlled release oxymorphone tablet on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. 9 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed

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by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. 9 in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)				
Hour	Oxymorphone		6-Hydroxyoxymorphone	
	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
15.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 10 in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)					
Day	Hour	Oxymorphone		6-Hydroxyoxymorphone	
		Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88

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TABLE 20-continued

Summary of Mean Plasma Concentration (ng/ml)					
Day	Hour	Oxymorphone		6-Hydroxyoxymorphone	
		Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
10	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
15	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results				
	Controlled Release 20 mg		Immediate Release 10 mg	
	oxy-morphone	6-OH-oxymorphone	oxy-morphone	6-OH-oxymorphone
AUC ₍₀₋₈₎	14.74	11.54	7.10	5.66
AUC _(0-inf)	15.33	16.40	7.73	8.45
C _{max} (ng/ml)	1.12	0.68	1.98	1.40
T _{max} (hr)	5.00	2.00	0.50	0.50
T _{1/2} (hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone AUC₍₀₋₈₎ values were lower than the parent compound after administration of either dosage form, but the AUC_(0-inf) values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma, concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified, using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

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It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5—Controlled Release 40 mg vs. Immediate Release 4.times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times.10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects

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received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5								
	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(0-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(0-inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(0-24)}$	
F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(0-24)}$	
F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

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The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone				
Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma 6-Hydroxyoxymorphone for Study 5								
	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(0-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(0-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and a controlled release delivery system comprising at least one pharmaceutical excipient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

2. The pharmaceutical composition of claim 1 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test.

3. The pharmaceutical composition of claim 1 wherein at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

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4. The pharmaceutical composition of claim 1 wherein the controlled release delivery system comprises a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid.

5. The pharmaceutical composition of claim 1 wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

6. The pharmaceutical composition of claim 5 wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

7. The pharmaceutical composition of claim 5 wherein the heteropolysaccharide comprises xanthan gum or deacylated xanthan gum.

8. The pharmaceutical composition of claim 5 wherein the agent capable of cross-linking the heteropolysaccharide comprises a homopolysaccharide gum.

9. The pharmaceutical composition of claim 8 wherein the homopolysaccharide gum comprises locust bean gum.

10. The pharmaceutical composition of claim 1 wherein the controlled release delivery system further comprises a hydrophobic polymer.

11. The pharmaceutical composition of claim 10 wherein the hydrophobic polymer comprises an alkylcellulose.

12. The pharmaceutical composition of claim 8 further comprising a cationic cross-linking agent.

13. The pharmaceutical composition of claim 12 wherein the cationic cross-linking agent is selected from calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and combinations thereof.

14. The pharmaceutical composition of claim 13 wherein the cationic cross-linking agent is present in an amount of about 0.5% to about 16%, by weight of the composition.

15. The pharmaceutical composition of claim 5 wherein the weight ratio of heteropolysaccharide to oxymorphone or pharmaceutically acceptable salt thereof is about 10:1 to about 1:10.

16. The pharmaceutical composition of claim 1 wherein oxymorphone or pharmaceutically acceptable salt thereof is present in an amount of about 5 mg to about 80 mg.

17. The pharmaceutical composition of claim 5 wherein the controlled release delivery system comprises about 10% to about 99% of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, about 1% to about 20% of a cationic crosslinking agent, and about 0% to about 89% of other ingredients which qualify as an inert pharmaceutical diluent, by total weight of the controlled release delivery system.

18. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 1 comprising about 5 mg to about 80 mg of oxymorphone or pharmaceutically acceptable salt thereof.

19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8

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at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

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20. The method of claim **18** wherein upon oral administration of the composition the oxymorphone $AUC_{(0-inf)}$ is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.

* * * * *



US008329216B2

(12) **United States Patent**
Kao et al.

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(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

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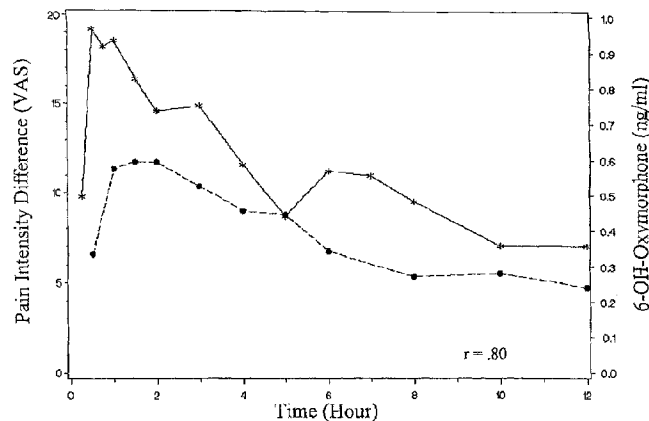
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(57) **ABSTRACT**

The invention pertains to a method of relieving pain by
administering a controlled release pharmaceutical tablet con-
taining oxymorphone which produces a mean minimum
blood plasma level 12 to 24 hours after dosing, as well as the
tablet producing the sustained pain relief.

82 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

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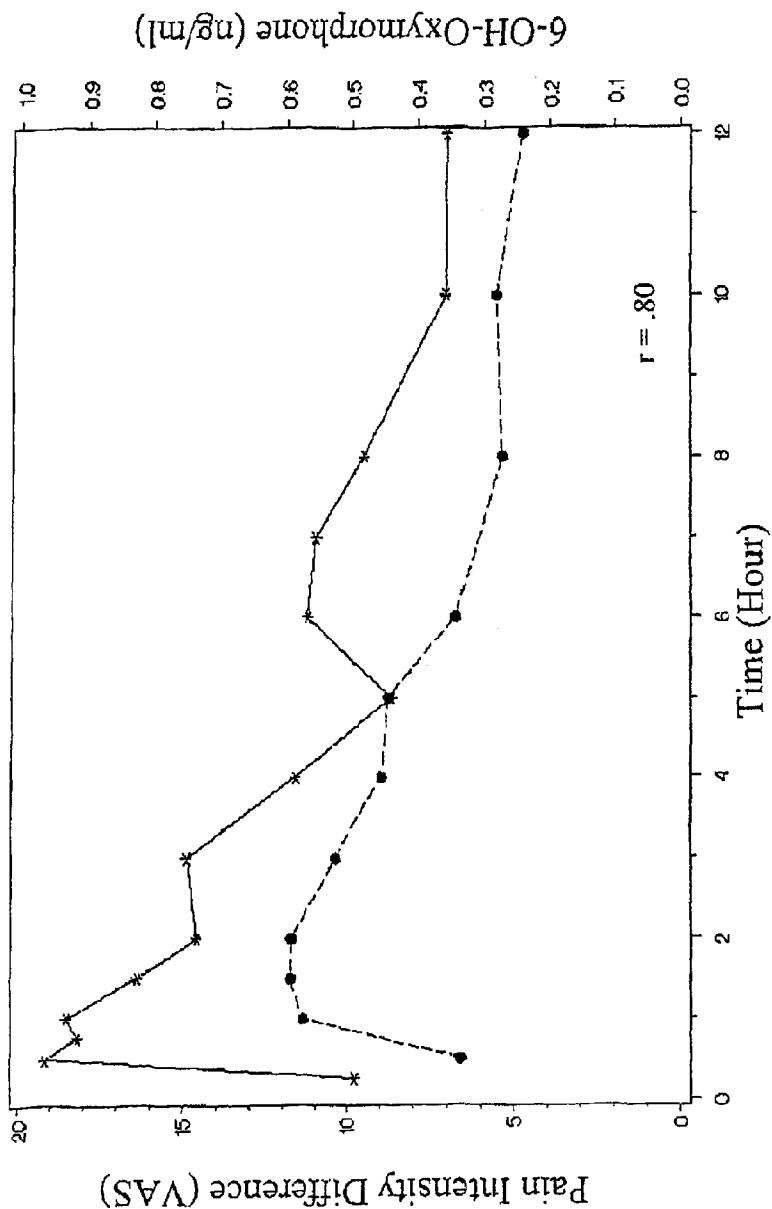
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PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations
Fig. 1

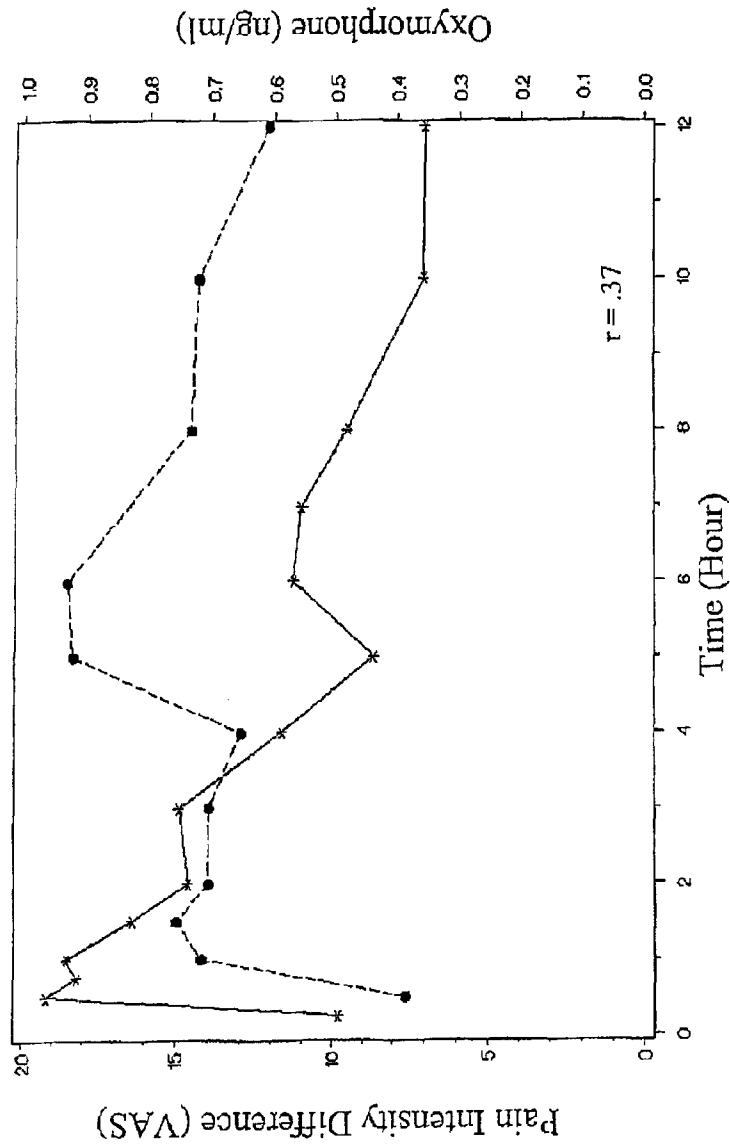
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PK Profile for Oxymorphone with PID Scores



* Pain Intensity Difference • Oxymorphone Plasma Concentrations

Fig. 2

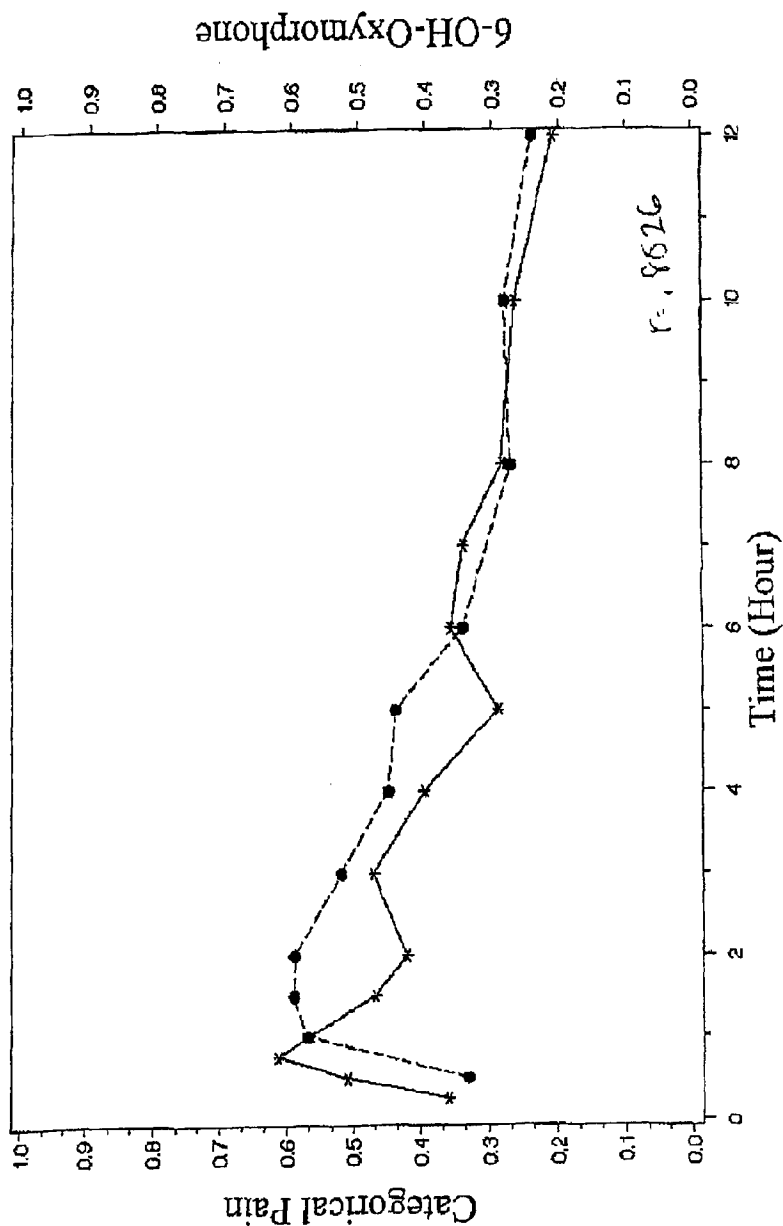
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PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores



* Categorical Pain ● 6-OH Oxymorphone Plasma Concentrations

FIG. 3

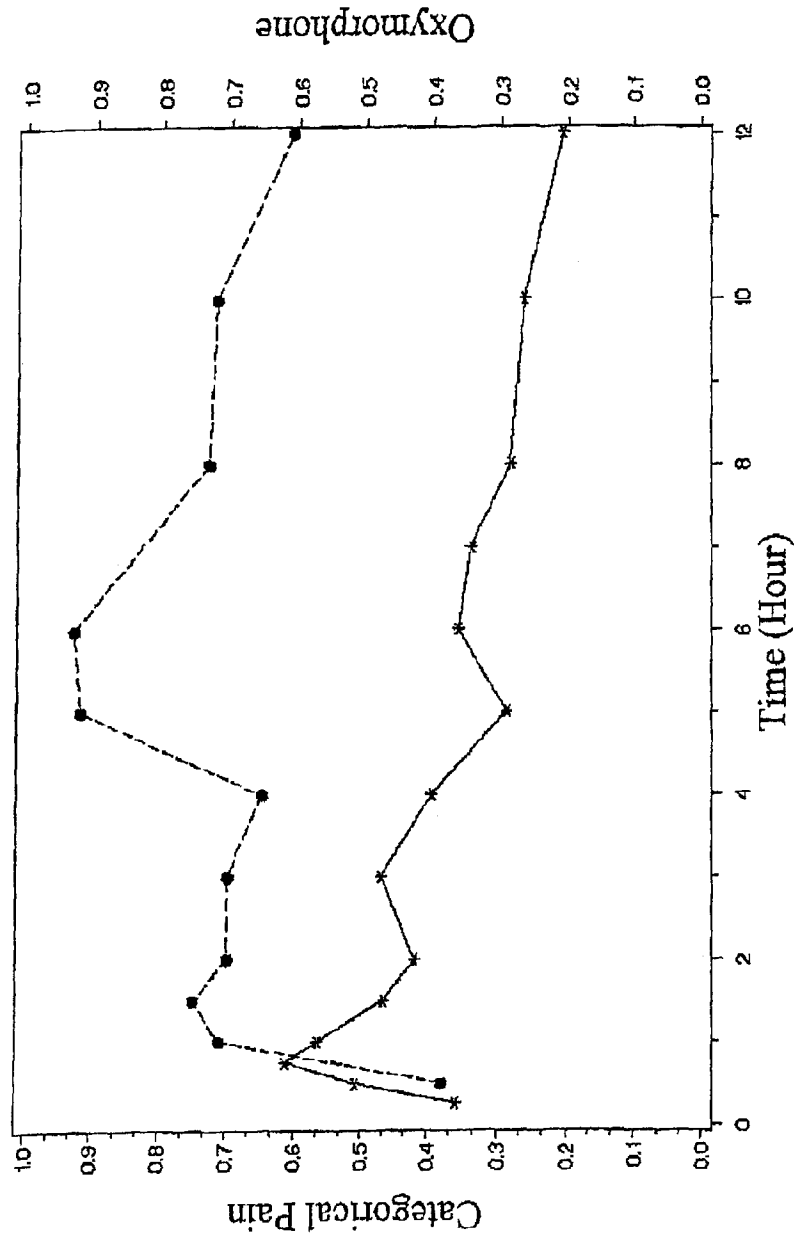
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PK Profile for Oxymorphone with Categorical Pain Scores



* Categorical Pain • Oxymorphone Plasma Concentrations

Fig. 4

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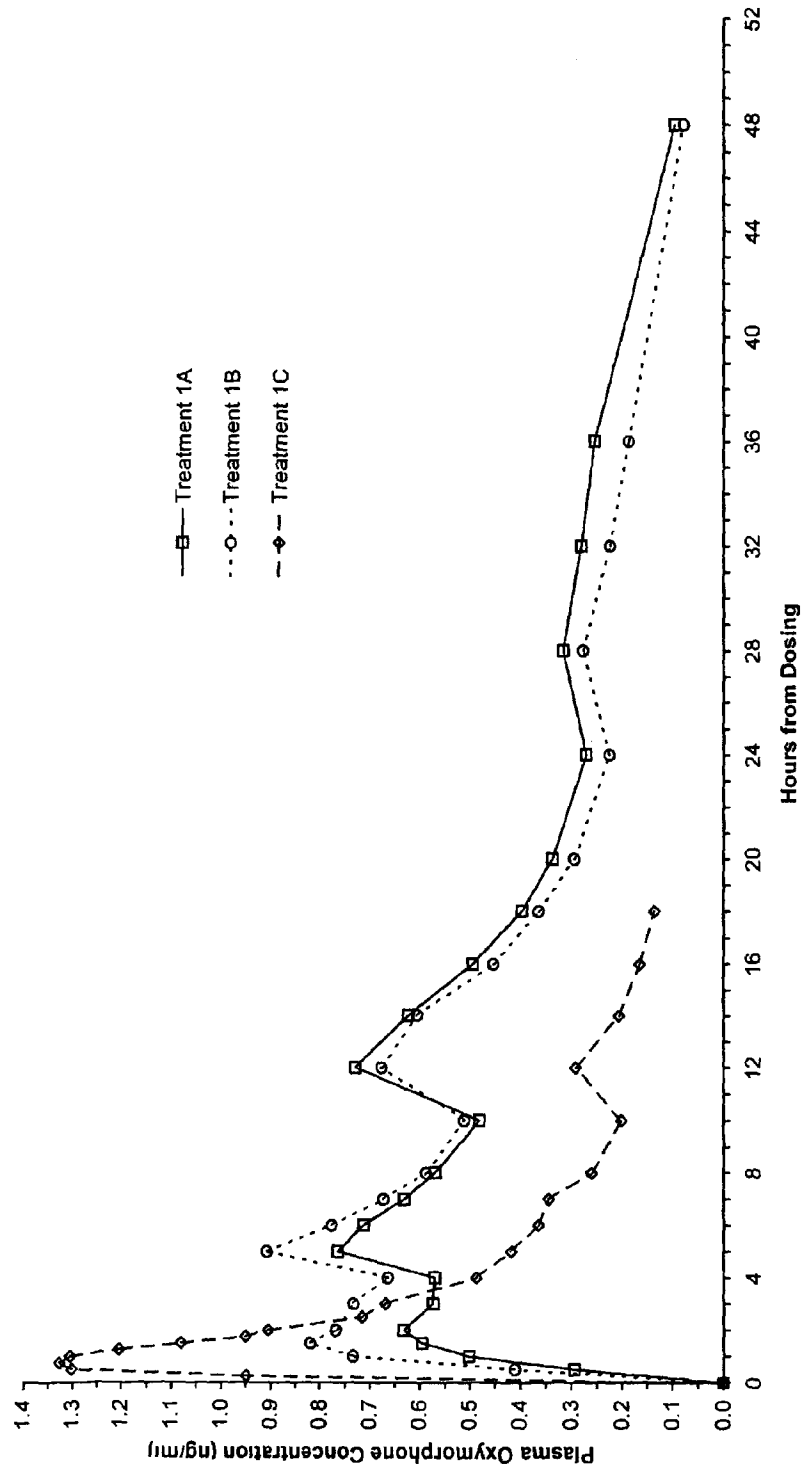


Figure 5

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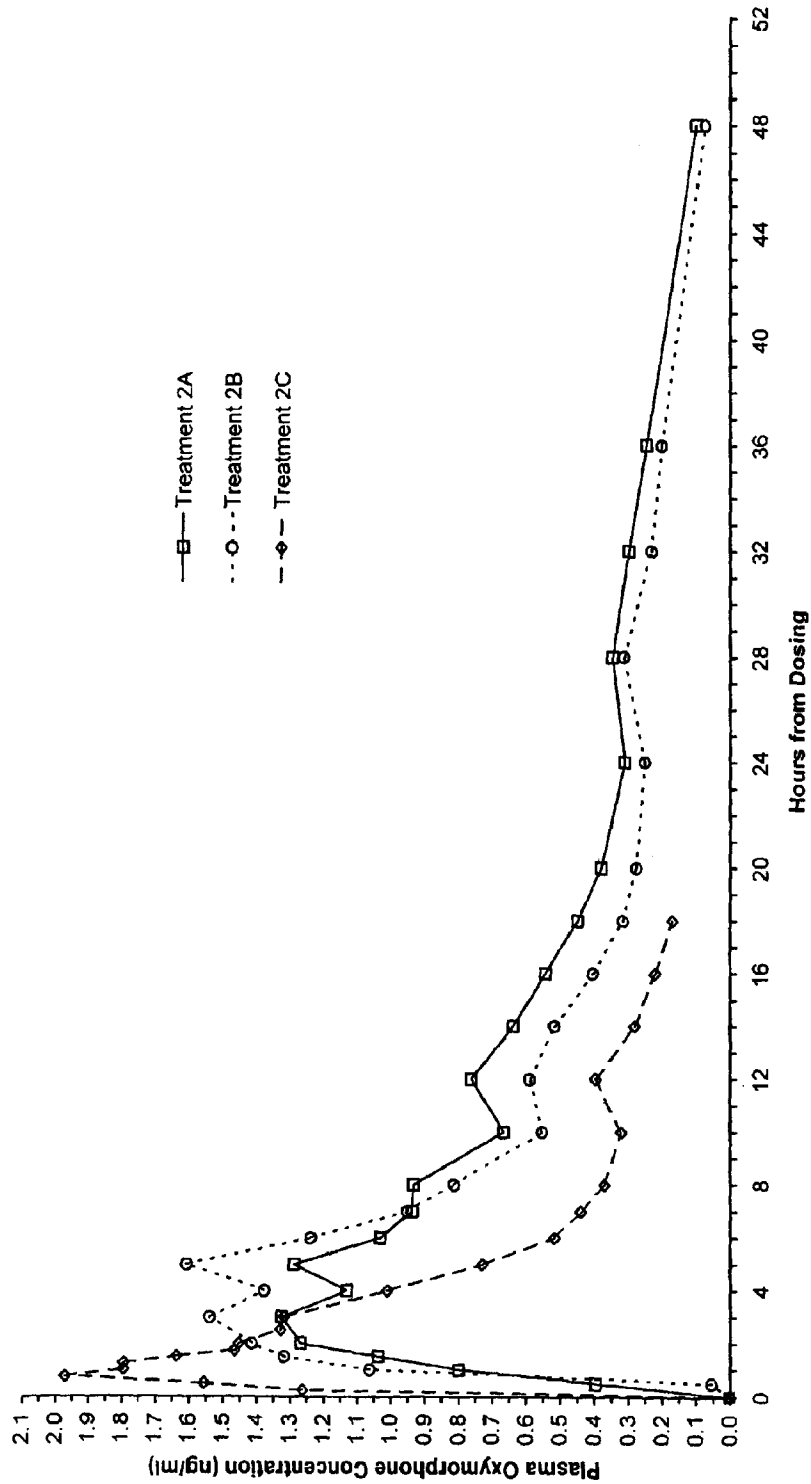


Figure 6

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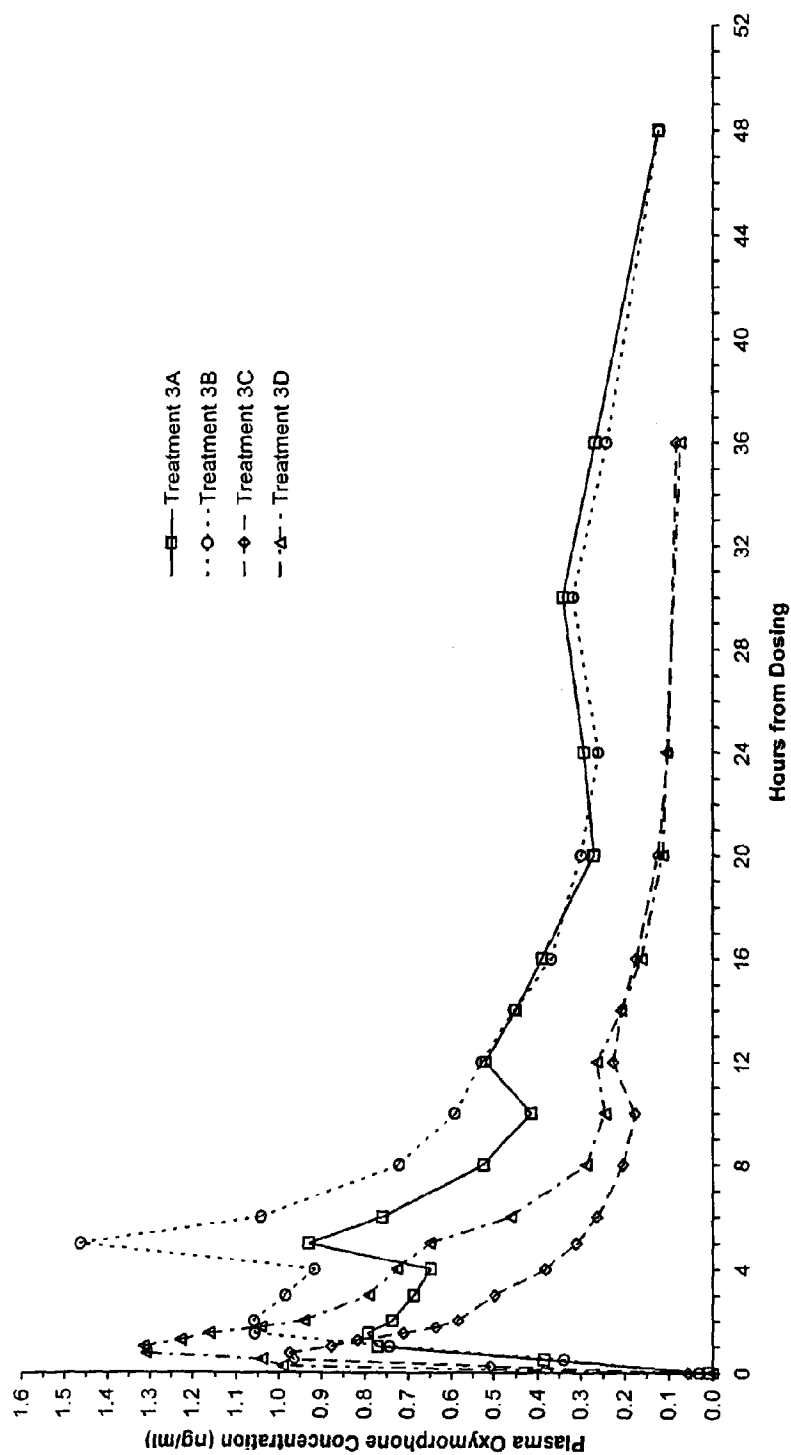


Figure 7

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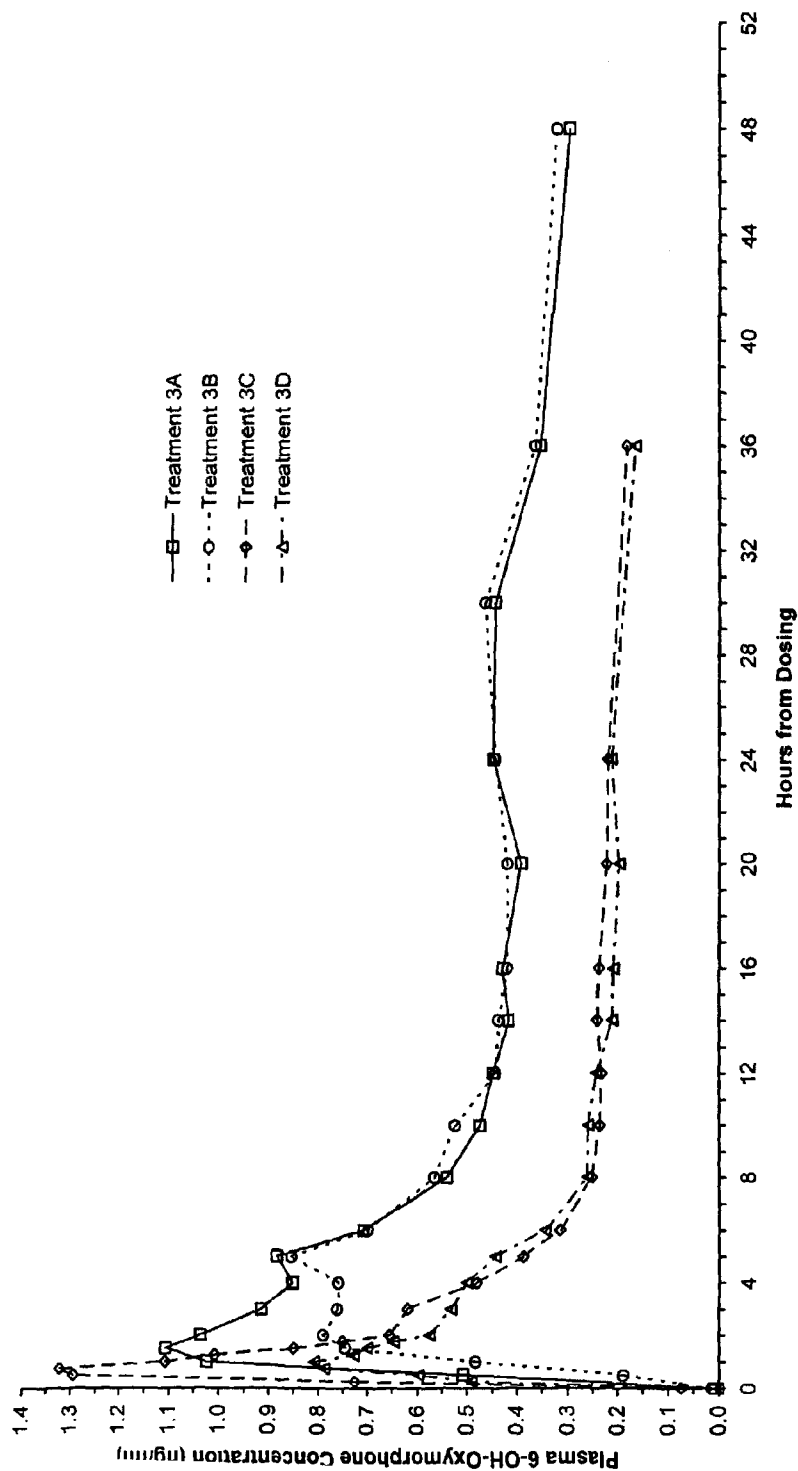


Figure 8

Appx305

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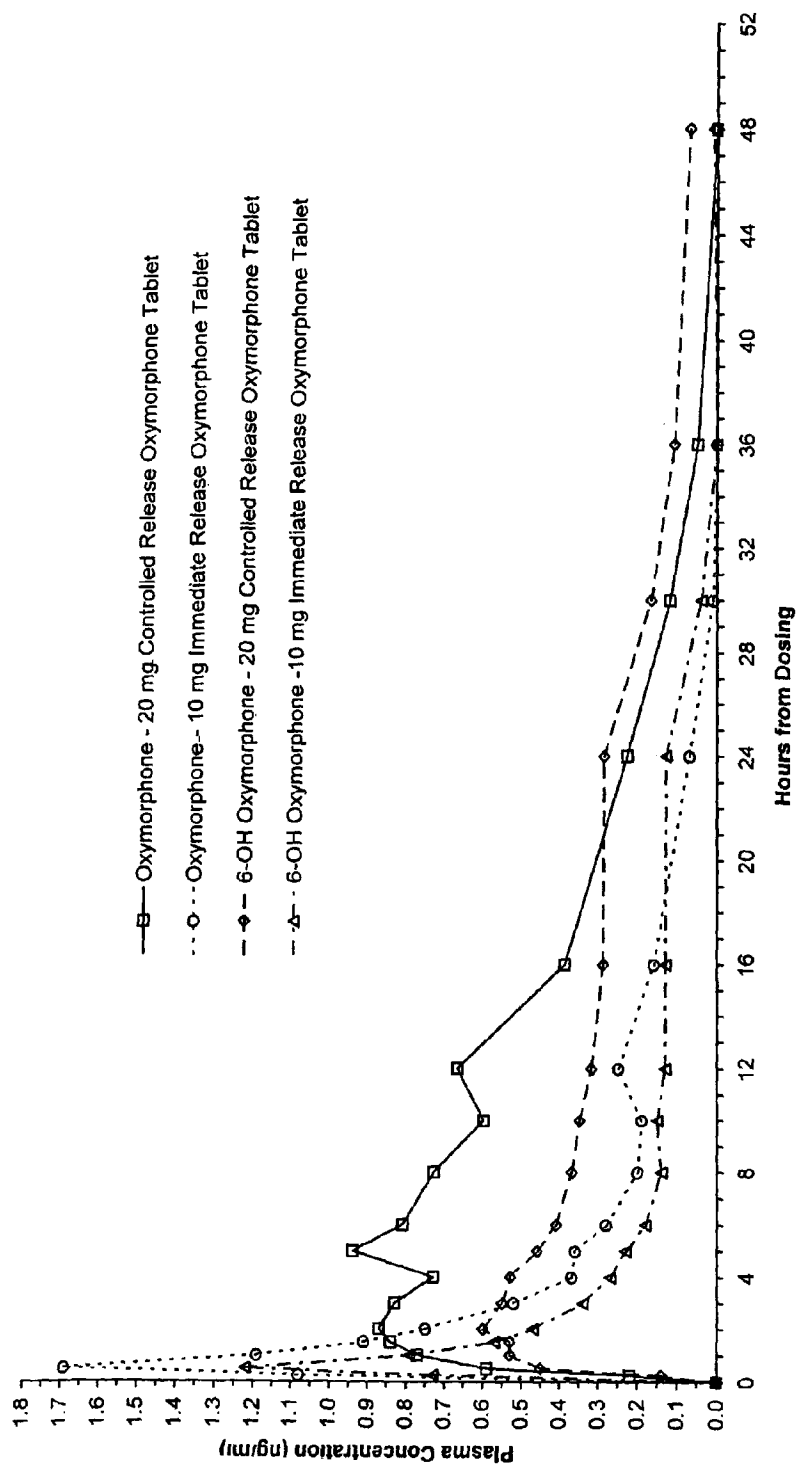


Figure 9

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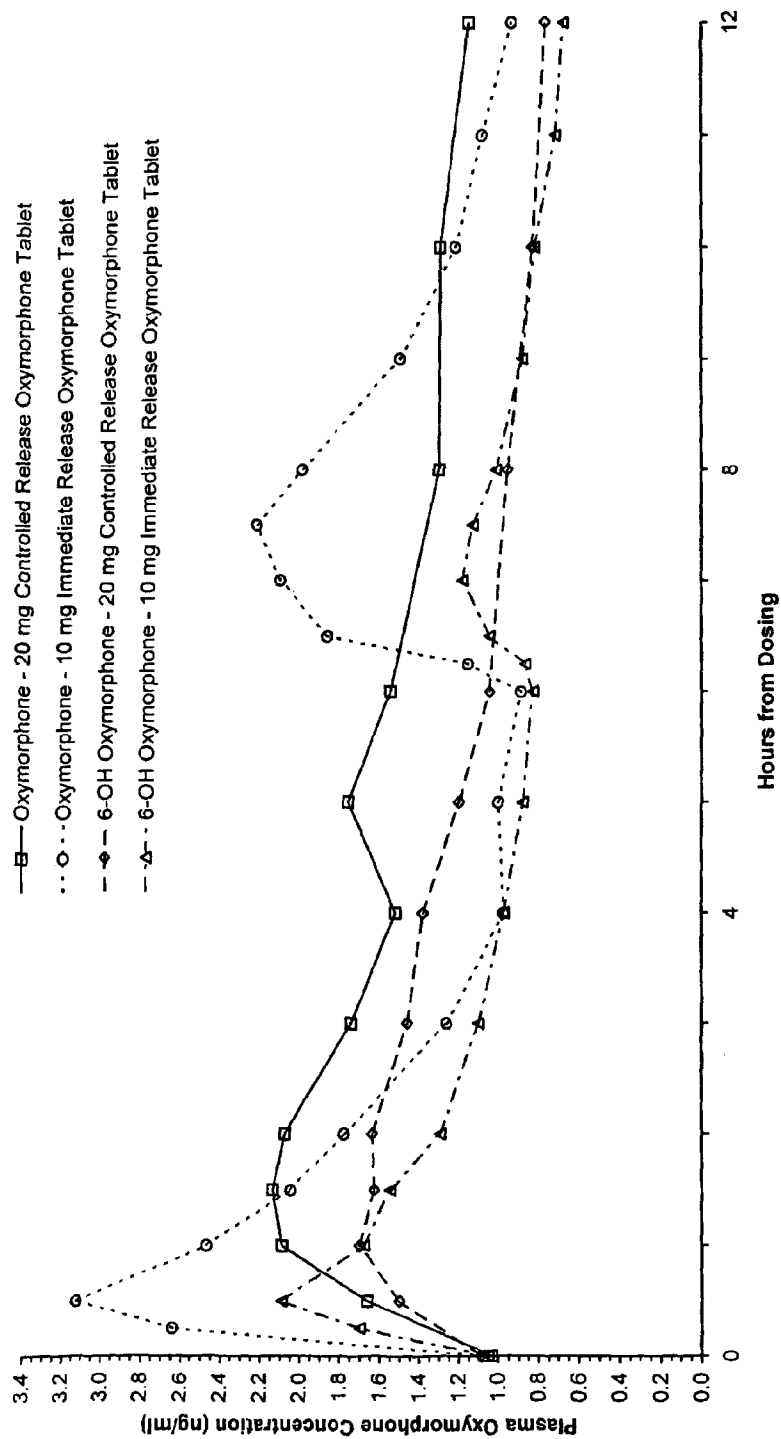


Figure 10

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OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**RELATED APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6- α - and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer

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patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. 2 is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. 3 is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. 4 is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. 5 is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. 6 is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. 7 is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. 8 is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. 9 is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. 10 is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

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ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values

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reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylene-sulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

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It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. 1-2 show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical

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ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

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and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^5$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacetylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially

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insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

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porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System		
Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10) ¹	(20.0) ¹
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

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TABLE 2

Sample Tablets of Differing Strengths					
Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, NF	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions			
Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets			
Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bio-availability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

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trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$ Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (C_t), calculated using linear trapezoidal summation.

$AUC_{(0-inf)}$ Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)} = AUC_{(0-t)} + C_t/K_{el}$, where K_{el} is the terminal elimination rate constant.

$AUC_{(0-24)}$ Partial area under the drug concentration-time curve from time zero to 24 hours.

C_{max} Maximum observed drug concentration.

T_{max} Time of the observed maximum drug concentration.

K_{el} Elimination rate constant based on the linear regression of the terminal linear portion of the LN (concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max} , $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive

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statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1—Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C	
0	0.000	0.000	0.0000	
0.25			0.9489	
0.5	0.2941	0.4104	1.3016	
0.75			1.3264	
1	0.5016	0.7334	1.3046	
1.25			1.2041	
1.5	0.5951	0.8192	1.0813	
1.75			0.9502	
2	0.6328	0.7689	0.9055	
2.5			0.7161	
3	0.5743	0.7341	0.6689	
4	0.5709	0.6647	0.4879	
5	0.7656	0.9089	0.4184	
6	0.7149	0.7782	0.3658	
7	0.6334	0.6748	0.3464	
8	0.5716	0.5890	0.2610	
10	0.4834	0.5144	0.2028	
12	0.7333	0.6801	0.2936	
14	0.6271	0.6089	0.2083	
16	0.4986	0.4567	0.1661	
18	0.4008	0.3674	0.1368	
20	0.3405	0.2970		
24	0.2736	0.2270		
28	0.3209	0.2805		
32	0.2846	0.2272		
36	0.2583	0.1903		
48	0.0975	0.0792		

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

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Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the time to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1						
	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-\infty)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61
Units:						
C_{max} in ng/ml,						
T_{max} in hours,						
AUC in ng * hr/ml,						
$T_{1/2el}$ in hours.						

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-\infty)}$			
F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)	
1.193 \pm 0.203	1.121 \pm 0.211	1.108 \pm 0.152	

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-18)}$			
F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)	
0.733 \pm 0.098	0.783 \pm 0.117	0.944 \pm 0.110	

Study 2-Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

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This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C	
0	0.000	0.000	0.0000	
0.25			1.263	
0.5	0.396	.0553	1.556	
0.75			1.972	
1	0.800	1.063	1.796	
1.25			1.795	
1.5	1.038	1.319	1.637	
1.75			1.467	
2	1.269	1.414	1.454	
2.5			1.331	
3	1.328	1.540	1.320	
4	1.132	1.378	1.011	
5	1.291	1.609	0.731	
6	1.033	1.242	0.518	
7	0.941	0.955	0.442	
8	0.936	0.817	0.372	
10	0.669	0.555	0.323	
12	0.766	0.592	0.398	
14	0.641	0.519	0.284	
16	0.547	0.407	0.223	
18	0.453	0.320	0.173	
20	0.382	0.280		
24	0.315	0.254		
28	0.352	0.319		
32	0.304	0.237		
36	0.252	0.207		
48	0.104	0.077		

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2						
	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-\infty)}$	22.89	5.486	21.34	5.528	21.93	5.044

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TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2						
	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
AUC _(0-inf)	25.28	5.736	23.62	5.202	24.73	6.616
T _{1/2rel}	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng • hr/ml,
T_{1/2rel} in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on AUC _(0-inf)		
F _{rel} (2A vs. 2C)	F _{rel} (2B vs. 2C)	F _{rel} (2A vs. 2B)
1.052 ± 0.187	0.949 ± 0.154	1.148 ± 0.250

TABLE 12

Relative bioavailability Determination Based on AUC _(0-18h)		
F _{rel} (2A vs. 2C)	F _{rel} (2B vs. 2C)	F _{rel} (2A vs. 2B)
0.690 ± 0.105	0.694 ± 0.124	1.012 ± 0.175

As may be seen from tables 5 and 10 and FIGS. 1 and 2, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T_{max} much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3-One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

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Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 7. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4653	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

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TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3								
	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.65	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-24)}$			
F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
1.040 \pm 0.1874	0.8863 \pm 0.2569	1.368 \pm 0.4328	1.169 \pm 0.2041

TABLE 16

Relative bioavailability Determination Based on $AUC_{(0-24)}$			
F_{rel} (3A vs. 2C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
0.9598 \pm 0.2151	0.8344 \pm 0.100	1.470 \pm 0.3922	1.299 \pm 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max} , but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from

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$AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max} (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max} was

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later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicated similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxy-

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ment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 8. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone				
Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3								
	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(0-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(0-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

morphine oral solution since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment.

Bioavailability of 6-hydroxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treat-

Study 4-Controlled Release 20 mg vs Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg

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controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. 9 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxyoxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 9 in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)				
Hour	Oxymorphone		6-Hydroxyoxymorphone	
	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.00	0.60	0.19	0.35	0.15
12.00	0.67	0.25	0.32	0.13
16.00	0.39	0.16	0.29	0.13
24.00	0.23	0.07	0.29	0.13
30.00	0.12	0.01	0.17	0.04
36.00	0.05	0.00	0.11	0.00
48.00	0.00	0.00	0.07	0.01

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FIG. 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 10 in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)					
Day	Hour	Oxymorphone		6-Hydroxyoxymorphone	
		Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.00	1.32	1.24	0.85	0.84
	11.00		1.11		0.74
	12.00	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results				
	Controlled Release 20 mg		Immediate Release 10 mg	
	oxymorphone	6-OH-oxymorphone	oxymorphone	6-OH-oxymorphone
AUC ₍₀₋₁₂₎	14.74	11.54	7.10	5.66
AUC _(0-12h)	15.33	16.40	7.73	8.45
C _{max} (ng/ml)	1.12	0.68	1.98	1.40
T _{max} (hr)	5.00	2.00	0.50	0.50
T _{1/2} (hr)	9.25	26.09	10.29	29.48

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Parent 6-OH oxymorphone $AUC_{(0-\infty)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(0-\infty)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg-ml) administered is measured. Thus at 0.02 ng/mg-ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5-Controlled Release 40 mg vs Immediate Release 4.Times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times.10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of

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oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24

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TABLE 22-continued

Mean Plasma Concentration vs. Time (ng/ml)				
Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5								
	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(0-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(0-inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$	
F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(0-24)}$	
F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone				
Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27

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TABLE 26-continued

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone				
Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma 6-Hydroxyoxymorphone for Study 5								
	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(0-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(0-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An oral controlled release oxymorphone formulation, comprising:

- about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
- a hydrophilic material,

wherein upon oral administration of the formulation to a subject in need of an analgesic effect:

- the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
- the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
- the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 \text{ to } inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;
- the duration of the analgesic effect is through at least about 12 hours after administration; and
- the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

2. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

3. The formulation of claim 1 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

4. The formulation of claim 3 wherein the gum is selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

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5. The formulation of claim 1 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

6. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

7. The formulation of claim 1 wherein the hydrophilic material comprises at least one of:

- i. a heteropolysaccharide; or
- ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or
- iii. a mixture of (i), (ii) and a polysaccharide gum.

8. The formulation of claim 7 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

9. The formulation of claim 7 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

10. The formulation of claim 7 wherein the cross-linking agent is a homopolysaccharide gum.

11. The formulation of claim 1 further comprising a hydrophobic polymer.

12. A method of treating pain in a subject in need thereof, the method comprising the step of administering to the subject the formulation of claim 1.

13. A pharmaceutical tablet prepared by:

- a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and controlled release granules comprising a hydrophilic material and one or more optional excipients; and
- b. directly compressing the mixture of (a) to form the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

14. The tablet preparation of claim 13 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

15. The tablet preparation of claim 13 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

16. The tablet preparation of claim 13 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

17. The tablet preparation of claim 13 wherein the hydrophilic material is hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

18. The tablet preparation of claim 13 wherein the hydrophilic material comprises at least one of:

- i. a heteropolysaccharide; or
- ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or
- iii. a mixture of (i), (ii) and a polysaccharide gum.

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19. The tablet preparation of claim 18 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

20. The tablet preparation of claim 19 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

21. A pharmaceutical tablet prepared by:

- a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and
- b. forming the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours.

22. The tablet of claim 21 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

23. The tablet of claim 21 wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

24. The tablet of claim 21, wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

25. The tablet of claim 21, wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

26. The tablet of claim 21, wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

27. The tablet of claim 21, wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

28. The tablet of claim 21, wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

29. The tablet of claim 21, wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

30. The tablet of claim 21, wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

31. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

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- (a) Providing a solid oral dosage form of a controlled release oxymorphone formulation with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and
- (b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.
32. The method of claim 31 wherein the dosage form comprises about 40 mg oxymorphone or a pharmaceutically acceptable salt thereof, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.
33. The method of claim 31 wherein the dosage form comprises about 20 mg oxymorphone or a pharmaceutically acceptable salt thereof.
34. The method of claim 31 wherein the dosage form comprises about 20 mg to about 40 mg oxymorphone hydrochloride.
35. The method of claim 31 wherein the difference in the oxymorphone area under the curve ($AUC_{(0-inf)}$) between fed and fasted conditions is less than 20%.
36. The method of claim 35 wherein the difference in $AUC_{(0-inf)}$ between fed and fasted conditions is about 18%.
37. The method of claim 31 wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:
- (i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
 - (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and
 - (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0-inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.
38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:
- (a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test; and

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- (b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.
39. The method of claim 38 wherein the oxymorphone C_{max} is at least about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.
40. The method of claim 38 wherein the difference in the oxymorphone area under the curve $AUC_{(0-inf)}$ between fed and fasted conditions is less than 20%.
41. The method of claim 40 wherein the difference in $AUC_{(0-inf)}$ between fed and fasted conditions is about 18%.
42. The method of claim 38 wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:
- (i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
 - (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and
 - (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0-inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.
43. The method of claim 38 wherein the system further comprises a hydrophilic material.
44. The method of claim 43 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.
45. The method of claim 44 wherein the hydrophilic material is a gum selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.
46. The method of claim 43 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.
47. The method of claim 43 wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.
48. The method of claim 43 wherein the hydrophilic material comprises at least one of:
- a. a heteropolysaccharide; or
 - b. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or
 - c. a mixture of (a), (b) and a polysaccharide gum.
49. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:
- a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and
 - b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient, wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°

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C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

50. The composition of claim 49 wherein upon oral administration thereof the oxymorphone $AUC_{(0-inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

51. The composition of claim 49 wherein the dosage form comprises about 40 mg oxymorphone, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

52. The composition of claim 49 wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

53. The composition of claim 52 wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

54. The composition of claim 49 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

55. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

- a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone over at least 12 hours to provide sustained pain relief over this same period; and
- b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

56. The composition of claim 55, wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions.

57. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

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58. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

59. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

60. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

61. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

62. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

63. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

64. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

65. The composition of claim 55, wherein the composition is in the form of a tablet and wherein at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

66. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

- a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and
- b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, and wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.

67. The composition of claim 66 wherein the blood plasma levels comprise two peaks.

68. The composition of claim 66 wherein upon oral administration of the composition to a subject in need of an analgesic effect:

- (i) the composition provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
- (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and
- (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 to inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

69. The composition of claim 66 wherein upon oral administration of the composition to a subject in need of an anal-

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gesic effect the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

70. The composition of claim 66 wherein upon oral administration of the composition to a subject in need of an analgesic effect the blood plasma levels of oxymorphone comprise a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration.

71. The composition of claim 66 wherein the composition is in the form of a tablet and about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

72. A controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test.

73. The pharmaceutical composition of claim 72 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

74. The pharmaceutical composition of claim 72 wherein at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

75. The pharmaceutical composition of claim 72 wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises one or peaks.

76. The pharmaceutical composition of claim 72 wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration; and wherein

- (i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
- (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
- (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 \text{ to } \infty)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and
- (iv) the duration of the analgesic effect is through at least about 12 hours after administration.

77. A controlled release pharmaceutical composition comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient, and a controlled release matrix comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

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wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test, and at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test,

wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0-\infty)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

78. The pharmaceutical composition of claim 77 wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect the blood plasma level of oxymorphone displays two or three peaks over about the first 12 hours after administration; and

- (i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
- (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
- (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0 \text{ to } \infty)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and
- (iv) the duration of the analgesic effect is through at least about 12 hours after administration.

79. The pharmaceutical composition of claim 77 wherein about 58% to about 66%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

80. The pharmaceutical composition of claim 77 wherein about 85% to about 96%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

81. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 72 in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof, wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0-\infty)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

82. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 77 in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof.

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Proof of Service

I hereby certify that on October 5, 2016, the foregoing APPELLANTS AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, AMNEAL PHARMACEUTICALS LLC, IMPAX LABORATORIES, INC., THORX LABORATORIES, INC., RANBAXY, INC., RANBAXY PHARMACEUTICALS, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., AND ROXANE LABORATORIES, INC.'S CORRECTED OPENING BRIEF was filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit using the appellate CM/ECF system which constitutes service on all parties represented by attorneys who have registered for the CM/ECF system, and that a copy was served on counsel of record for all parties via e-mail.

Dated: October 5, 2016

By: /s/Brenda L. Joly
Brenda L. Joly
Counsel for Appellants Amneal
Pharmaceuticals of New York LLC
and Amneal Pharmaceuticals LLC

**Certificate of Compliance
with Type-Volume Limitation, Typeface Requirements,
and Type Style Requirements**

The undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 13,769 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

The undersigned also hereby certifies that this brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Office Word 2010 in 14-point Book Antiqua type style, with 14-point or larger Book Antiqua type style headings.

As permitted by Federal Rule of Appellate Procedure 32(a)(7)(C)(i), the undersigned has relied upon the word count of this word processing system in preparing this certificate.

Dated: October 3, 2016

By: /s/ Brenda L. Joly
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